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# ENHANCED RECOVERY AFTER SURGERY (ERAS) INTERVENTIONS AND OUTCOME FROM COLORECTAL SURGERY

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Stockholm 2021

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Published by Karolinska Institutet.
Printed by US-AB 2020

ISBN 978-91-7831-950-3

# Enhanced Recovery After Surgery (ERAS) interventions and outcome from colorectal surgery

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“I HATED EVERY MINUTE OF TRAINING, BUT I SAID ‘DON’T QUIT’. SUFFER NOW AND LIVE THE REST OF YOUR LIFE AS A CHAMPION”

*MUHAMMAD ALI*

*To Helena*

# ABSTRACT

Although immense progress has been made in the fields of chemo- and radiotherapy during the last decades, surgery is still the ultimate cure for the majority of patients with colorectal cancer. Since colorectal cancer most often presents at a high age and in patients often suffering from a large burden of comorbidity, it is important to develop strategies to improve postoperative recovery and outcome, not only for the patient, but also from a health economic perspective.

ERAS (Enhanced Recovery After Surgery) is an evidence-based concept aiming to reduce surgical stress, shown to reduce perioperative morbidity, improve postoperative recovery and shorten length of stay (LOS). Today, the international ERAS® Society Interactive Audit System (EIAS) includes a database containing more than 80 000 patients, each patient with more than 300 perioperative variables recorded. The database is a valuable source for research and a guide for surgical centres to sustain and improve principles of perioperative care.

Within the research field of ERAS, our research group identified two major questions that need further investigation. First, single interventions included in the ERAS protocol require further evaluation regarding the impact on the protocol as a whole. Second, most studies have so far been focusing on short-term outcomes after surgery. The effect of an ERAS-program on long-term outcome is however, largely unknown.

The overall aim of this thesis was to investigate these topics and hopefully fill some of the knowledge gaps concerning these questions.

In **paper I** we evaluated the effect of perioperative fluid management on short-term postoperative outcomes and 5-year survival after surgery. This single-center cohort study included patients with colorectal cancer operated between 2002 to 2007. In all, 911 patients were enrolled. Patients receiving < 3000 mL iv fluid on the day of surgery were compared with patients receiving > 3000 mL. A restrictive fluid management was associated with shorter LOS (mean 5.6 vs 9.0 days, $p < 0.001$), lower risk of complications (odds ratio (OR) 0.44, 95 % confidence interval (CI) (0.28 – 0.71)) and symptoms delaying discharge (OR 0.47, 95 % CI (0.32 - 0.70)). The risk of cancer specific death was significantly reduced (hazard ratio (HR) 0.45, 95 % CI (0.25 – 0.81)). The study concluded a possible association between a restrictive fluid regimen and improved short- and long-term outcomes.

In **paper II** the aim was to compare robotic and laparoscopic rectal tumor surgery within an ERAS setting regarding short-term outcomes and compliance to the ERAS protocol. This single-center cohort study included 47 patients operated with laparoscopic technique between January 2011 to April 2014 and 72 patients operated with robotic technique between April 2014 to January 2017. Robotic surgery was associated with shorter LOS (median 3 vs 7 days, $p < 0.001$), lower rate of complications (25 % vs 49 %, $p < 0.01$) and a lower conversion rate to open surgery (11 % vs 34 %, $p = 0.002$). Results endured in multivariate analysis. Compliance to the ERAS protocol showed no difference between groups. The conclusion, in

this single-center cohort study, was that robotic rectal tumor surgery demonstrated superior short-term outcomes compared to laparoscopic rectal tumor surgery.

In **paper III** the Swedish part of the international ERAS database was used to compare short-term outcome in patients operated on with robotic, laparoscopic and open rectal tumor surgery. Compliance to the ERAS® Society Guidelines was compared between groups. This multi-center retrospective cohort study included 3125 patients between January 2010 to February 2020. Robotic surgery showed similar complication rates compared to open surgery (35.9 % vs 40.9 %, OR 1.15, 95% CI (0.93, 1.41)) and laparoscopic surgery (35.9 % vs 31.2 %, OR 0.88, 95% CI (0.71, 1.08)). LOS was shorter in the robotic group, median 6 days vs 9 days in the open group (incidence rate ratio (IRR) 1.35, 95% CI (1.27, 1.44)) and 7 days in the laparoscopic group (IRR 1.14, 95% CI (1.07, 1.21)). Robotic surgery had a lower conversion rate compared to laparoscopic surgery (8.3 % vs 18.0 %, OR 2.58, 95 % CI (1.85, 3.60)). Pre- and intraoperative compliance to the ERAS protocol were similar between groups. In conclusion, this multi-center cohort study demonstrated shorter LOS in robotic surgery vs open and laparoscopic surgery and lower conversion rate to open surgery in the robotic group vs the laparoscopic group.

In **paper IV** the aim was to identify predictors for anastomotic leakage (AL) in patients operated with anterior resection (AR) included in the Swedish part of the international ERAS database. Altogether 1900 patients were investigated between January 2010 to February 2020, 155 patients with AL and 1745 patients without AL. Obesity (OR 1.71, 95 % CI (1.04, 2.80)), male gender (OR 1.88, 95 % CI (1.28, 2.75)), duration of primary surgery (OR 1.13, 95 % CI (1.02, 1.24)), peritoneal contamination (OR 1.78, 95 % CI (1.01, 3.16)) and surgery late in the study period (OR 1.89, 95 % CI (1.18, 3.01)) were all independent predictors for AL. Patients suffering from AL had longer LOS (median 7 vs 15 days, $p < 0.001$) and higher rate of reoperations (69.7 % vs 6.6 %, $p < 0.001$) compared to patients without AL. No difference in pre- and intraoperative compliance was seen between groups. In conclusion, this multi-center cohort study showed that male gender, obesity, duration of surgery, surgery late in the study period and peritoneal soiling were independent predictors for AL.

# LIST OF SCIENTIFIC PAPERS

I. **Daniel Asklid**, Josefin Segelman, Claes Gedda, Fredrik Hjern, Klas Pekkari, Ulf O Gustafsson

   **The impact of perioperative fluid therapy on short-term outcomes and 5-year survival among patient undergoing colorectal surgery – A prospective cohort study within an ERAS protocol**
   (*Eur J Surg Oncol. 2017 Aug;43(8):1433-1439*)

II. **Daniel Asklid**, Roger Gerjy, Fredrik Hjern, Klas Pekkari, Ulf O Gustafsson

   **Robotic vs laparoscopic rectal tumour surgery: a cohort study**
   (*Colorectal Dis. 2019 Feb;21(2):191-199*)

III. **Daniel Asklid**, Olle Ljungqvist, Yin Xu, Ulf O Gustafsson

   **Short-term outcome in robotic vs laparoscopic and open rectal tumor surgery within an ERAS protocol. A retrospective cohort study from the Swedish ERAS-database**
   (submitted manuscript)

IV. **Daniel Asklid**, Olle Ljungqvist, Yin Xu, Ulf O Gustafsson

   **Risk factors for anastomotic leakage in patients with rectal tumor operated with anterior resection within an ERAS protocol. A retrospective cohort study from the Swedish ERAS-database**
   (submitted manuscript)

## CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ERAS | Enhanced Recovery After Surgery |
| LOS | Length of stay |
| EIAS | ERAS®Society Interactive Audit System |
| OR | Odds ratio |
| CI | Confidence interval |
| HR | Hazard ratio |
| IRR | Incidence rate ratio |
| AL | Anastomotic leakage |
| AR | Anterior resection |
| FAP | Familial adenomatous polyposis |
| APC | Adenomatous polyposis coli |
| TME | Total mesorectal excision |
| CME | Complete mesocolic excision |
| 5-FU | 5-Fluorouracil |
| LV | Leucovorin |
| TNFα | Tumor necrosis factor-alpha |
| CNS | Central nervous system |
| RCT | Randomized controlled trial |
| PONV | Prevention of nausea and vomiting |
| WHO | World Health Organization |
| Hb | Hemoglobin |
| ESA | Erythropoiesis-stimulting agent |
| MBP | Mechanical bowel preparation |
| SSI | Surgical site infection |
| GDFT | Goal-directed fluid therapy |
| POI | Postoperative ileus |
| MIS | Minimally invasive surgery |
| CRM | Circumferential resection margin |

| | |
|---|---|
| BMI | Body Mass Index |
| NSAID | Non-steroidal anti-inflammatory drug |
| DS | Diverting stoma |
| SD | Standard deviation |
| ASA | American Society of Anaesthesiologists |
| NNT | Numbers needed to treat |
| APR | Abdominoperineal resection |
| CRC | Colorectal cancer |

# 1 BACKGROUND

## 1.1 COLORECTAL CANCER

### 1.1.1 Epidemiology

Colorectal cancer is the third most common form of cancer worldwide, second only to lung and breast cancer, accounting for approximately 1.8 million new cases per year. About 0.9 million people die from the disease each year, making colorectal cancer the second most common cause of cancer-related death in the world today[1, 2]. Western Europe, Australia and New Zeeland show the highest incidence, compared to a low incidence in Africa[1].

Colorectal cancer is mostly a disease appearing at high age, with only about 5 % of the cases presenting before the age of 40[3]. Median age at diagnosis, for colorectal cancer overall, is 70 years[4]. Rectal cancer accounts for 35 % of all colorectal cancer incidence. Globally, the incidence of right-sided colon cancer is increasing[5, 6] and there are data describing an increased incidence in left-sided tumors and rectal cancers in younger people, under age 50[7, 8].

### 1.1.2 Aetiology

Adenocarcinoma of the colon and rectum is thought to have its origin from an existing preneoplastic adenoma[9-11]. The development from a benign adenoma to a malignant tumor probably take many years and involves several mutations in the mucosal DNA. This accumulation of mutations, ultimately resulting in malignant transformation, is called the adenoma-carcinoma sequence, a theory that was published in 1990[12]. The prevalence of colonic adenomas in the U.S. population older than 50 years is estimated to 20-53 % and adenocarcinoma 0.2-0.6 %, suggesting that most adenomas are static or even regress with time. Risk for developing cancer or high-grade dysplasia is related to the size of the adenoma, where adenomas larger than 10 mm are considered more prone to malignant transformation[10, 13].

Age is probably the most important risk factor for developing colorectal cancer[14], but as for most other forms of malignancy, there is no known single triggering factor for the disease. However, environmental, inflammatory and hereditary factors all seem to play a part in the development.

Well known environmental risk factors are smoking[15-17], alcohol[18, 19] and overweight[20]. Publications have demonstrated a correlation between red meat and colorectal cancer[21]. Physical activity, fruits and vegetables might have a protective effect[22-25], while diabetes increases the risk of developing colorectal cancer. This might explain part of the association between obesity and colorectal cancer, since diabetes is overrepresented in obese people[26]. Patients suffering from long-standing ulcerative colitis[27] and Mb Crohn[28] are at increased risk of developing colorectal malignancy[29]. Furthermore, data on association between the gut bacterial microbiome and colorectal cancer is emerging where E.Coli and Fusobacterium in increased quantity are seen as potential risk factors in developing cancer in the colon and rectum[30, 31].

In most cases (70-80 %) colorectal cancer appears as sporadic disease. Hereditary factors cause or affect up to 20-30 %, but only in 2-8 % of the cases a single gene is found as the triggering factor for the disease. In these patients, which are identified by investigating potential family history of the disease, the tumor is caused by germline mutations, correlated with a high risk for malignant development[32-34].

The most common hereditary syndromes are Lynch syndrome and Familial adenomatous polyposis (FAP). Lynch syndrome is estimated to account for about 3 % of colorectal cancer cases and is caused by germline mutations in mismatch repairgenes[35-37]. These mutations give rise to errors in replicating repetitive DNA sequences and induce microsatellite instability[38, 39]. Endometrial cancer, ovarian and stomach tumors can appear in patients with this syndrome as well[40]. Lifetime risk of developing cancer is 70-90 %[41].

FAP is attributed to a germline mutation in the adenomatous polyposis coli (APC) gene. About 1 % of colorectal cancer cases is caused by FAP and it will inescapably lead to cancer if left without treatment[42]. FAP is characterized by multiple polyps and patients are screened for cancer from young age.

### 1.1.3 Diagnostics

Changes in otherwise stable bowel habits, anemia and blood in the stool should rise early suspicion of colorectal cancer, but a tumor can also remain asymptomatic until reaching an advanced stage. Rectal bleeding in persons older than 45 years should prompt lead to colonoscopy or CT colonography[43].

Colonoscopy or CT colonography are mandatory when suspecting intestinal malignancy where colonoscopy has the advantage of superior accuracy for small lesions and enables biopsies for pathology diagnosis. These investigations are also important in detecting synchronous cancers, existing in about 2 – 4 % of cases[1, 44]. With this knowledge, visualization of the entire colon should be completed postoperatively, if for some reason not possible before the operation. For rectal cancer, it is mandatory to perform rectoscopy to define the exact distance from the anal verge. This is important in decision making regarding choice of surgical approach and neoadjuvant therapy.

When deciding on neoadjuvant treatment, staging of the tumor is also important, especially in rectal cancer. In tumor staging, MRI and CT scan are preferred methods[45, 46]. Twenty percent of patients diagnosed with colorectal cancer present with distal metastasis[47], most common in the liver, hence imaging of the liver should be done for all patients. Sensitivity of MRI is slightly higher than CT[48]. Lung metastasis appear in about 2 % of newly diagnosed colorectal cancer patients[49]. Staging should therefore also include a chest CT.

A multidisciplinary team conference, where surgeons, radiologists, pathologists and oncologists discuss and recommend treatment for each patient with colorectal cancer, is today considered a requirement for treating patients with colorectal cancer. Assessment by multidisciplinary teams is associated with better outcome[50-52].

### 1.1.4 Surgical treatment

Surgery is the primary treatment for colorectal cancer, since a curative resection most often is needed for long-term survival. For rectal cancer, TME (total mesorectal excision) removing the mesorectum with embedded lymph nodes, resulting in improved survival outcome, is advocated[53, 54]. In colorectal cancer surgery, reliable staging requires at least 12 lymph nodes, since an increasing number of detected lymph nodes is considered a favourable prognostic sign[4]. In this aspect however, it is not demonstrated whether a ”hight-tie” ligation of the central blood vessel, i.e. a more radical extirpation of lymph drainage, is related to prolonged survival[55]. In addition, increased risk of local recurrence and distant metastasis have been demonstrated in patients with involved circumferential margin in rectal cancer surgery[56, 57]. For same reasons, CME (complete mesocolic excision) may be recommended in colon cancer surgery, yielding superior specimen and including increased number of lymph nodes[58].

### 1.1.5 Radiation therapy for rectal cancer

The previous high rate of local recurrence has decreased since the introduction of TME surgery[59], but neoadjuvant therapy still remains important. The rate of local recurrences decrease even more after neoadjuvant radiotherapy[60, 61, 62] due to downstaging of the tumor, promoting better outcome after surgery, i.e. to facilitate micro- and macro radical (R0) resection. There are two principal treatment schedules, long-course radiotherapy (a radiation dose of 1.8 Gy per day up to 28 fractions), or short-course radiotherapy (5 Gy x 5).

In Sweden, short-course radiotherapy has for many years been followed by immediate surgery, but recently, a 6-10 week interval, with intention to downsize the tumor, has been the first choice[63] of treatment. Long-course radiotherapy is often combined with oral fluoropyrimidine (Capecitabine), acting as a radio-sensitizer. When combined, studies have shown a decrease in local recurrence rate, but benefit in terms of increased survival rate is lacking[64]. Neoadjuvant radiotherapy is chosen over adjuvant radiotherapy since reduced rates of local recurrences and toxic effects have been shown comparing the two regims[65]. Radiation therapy for colon cancer has not showed any benefits in terms of either survival or local recurrence[66].

Rectal cancer can be staged in to three different groups when considering neoadjuvant therapy – ”good”, ”bad” and ”ugly” (Table 1). Good tumors are in no need of preoperative treatment and can proceed to surgery alone. Bad tumors will ordinarily require short-course radiotherapy while ugly tumors generally will receive chemoradiotherapy[67].

*Table 1. Rectal tumors based on radiological TNM staging[67]*

| | **Good** | **Bad** | **Ugly** |
|---|---|---|---|
| **Low tumor** (< 8 cm) | T1-2, N0, MRF- | T3, N1-2, MRF- | T4, T3, MRF+ |
| **High tumor** (> 8 cm) | T1-T3b, N0, MRF- | T3c-d, N1-2, MRF- | Lateral nodes |

T – invasiveness of the primary tumor, N – lymph node status, MRF – mesorectal fascia

In recent years, the concept of “watch-and-wait” has been implemented in clinical practice. This, since neoadjuvant radiotherapy (alone or combined with chemotherapy) has been shown to achieve complete clinical and radiological response in up to 20 % of localized rectal cancer cases. The concept includes close monitoring of patients and has so far been proven safe with encouraging outcomes[68].

### 1.1.6 Adjuvant chemotherapy

Adjuvant chemotherapy may eliminate remaining micrometastases and thereby reduce the risk of overall cancer recurrence[43]. Cornerstones of adjuvant therapy are 5-Fluorouracil (5-FU) combined with leucovorin, acting as a modulator or the oral prodrug (Capecitabine) and Oxaliplatin. Five year survival for stage III colon cancer after surgery can reach as high as 60 %[69]

(Table 2) where survival rate is increased by 15% and recurrence rate is decreased by 17 % in patients treated with 5-FU based adjuvant therapy compared to no chemotherapy at all[70]. Several studies, including the MOSAIC study, have demonstrated survival benefits adding Oxaliplatin to 5-FU/LV[70-73], but a major drawback related to this drug is the increased risk of peripheral neuropathy[74].

*Table 2. TNM classification[75]*

| Stage | T | N | M |
|---|---|---|---|
| **0** | Tis | N0 | M0 |
| **I** | T1-2 | N0 | M0 |
| **IIA** | T3 | N0 | M0 |
| **IIB** | T4a | N0 | M0 |
| **IIC** | T4b | N0 | M0 |
| **IIIA** | T1-2 | N1/N1c | M0 |
| | T1 | N2a | M0 |
| **IIIB** | T3-T4a | N1/N1c | M0 |
| | T2-T3 | N2a | M0 |
| | T1-T2 | N2b | M0 |
| **IIIC** | T4a | N2a | M0 |
| | T3-T4a | N2b | M0 |
| | T4b | N1-N2 | M0 |
| **IVA** | Any T | Any N | M1a |
| **IVB/C** | Any T | Any N | M1b |

T – invasiveness of the primary tumor, N – lymph node status, M – metastases

In stage II (node negative) cancers, surgery will usually provide cure, however up to 30 % will eventually develop disease recurrence[76]. Several studies[70, 77] have shown trends toward better survival in individuals given adjuvant chemotherapy. Adjuvant therapy is therefore considered in patients with stage II disease having one or more high risk variables such as: T4 stage, perforated or obstructing tumor, fewer than 12 nodes analyzed, vascular or perineural invasion or emergency surgery[14, 69, 78].

Evidence regarding the benefit of adjuvant therapy in rectal cancer patients is however largely missing since results from studies on survival are conflicting[79-81]. Despite this, in clinical reality, some rectal cancers are treated similarly as colon cancers, i.e. stage III and high-risk stage II cancer patients without contraindications are offered adjuvant therapy.

Adjuvant chemotherapy should start within 8 weeks after surgery to achieve optimal outcome[82]. The duration of treatment is usually six months, although data on three months treatment have demonstrated lower toxicity without compromising treatment efficacy[83].

## 1.2 SURGICAL STRESS AND PATHOPHYSIOLOGY

Regulation of normoglycemia requires a balanced hepatic glucose production in addition to an ordered glucose uptake by tissues of the body. This balance is to a large extent maintained by insulin, the major anabolic hormone in humans.

The effect of surgery can be described similar to a traumatic injury to the patient. In response to surgery, the body is set in a catabolic state, followed by destruction of body tissue, release of glucose, amino acids and fatty acids into the bloodstream, altering glucose, insulin and protein metabolism[84, 85]. Surgical trauma activates the sympathetic nervous system, as well as the hypothalamopituitary axis, triggering release of counter-regulatory hormones, such as catecholamines, cortisol, glucagon and growth hormone and cytokines (IL-1, IL-6 and tumor necrosis factor-alpha (TNF$\alpha$)), resulting in insulin resistance and elevated blood glucose levels[85].

Reduced sensitivity to insulin in tissues of the body, i.e. insulin resistance, is regarded one of the main underlying factors behind the body's destructive response to surgery[86, 87].

Although the complete mechanism behind insulin resistance and catabolism is yet to be discovered, insulin resistance has been described to induce release of proinflammatory cytokines, generate oxidative stress and have a negative effect on the immune system[88-91]. The skeletal muscle is the principle site for trauma-induced insulin resistance, since it represents the largest part of insulin-mediated glucose uptake. Catabolism in muscles leads to protein breakdown and release of amino acids used by the liver to produce glucose as energy and to generate the base for protein synthesis in the wound and liver[92-95].

These factors changing metabolism, ultimately result in apoptosis and cell dysfunction rendering worse recovery[88, 91]. In addition, studies have shown increased number of infections, longer length of stay (LOS) and even higher mortality rates in patients with an elevated blood glucose level after surgery[96]. Elevated Hemoglobin A1c, a marker for glucose control of the preceding 3 months, has also been described as a possible risk factor for complications after surgery[97, 98].

Figure 1 illustrates the theory behind surgical stress, insulin resistance and catabolism.

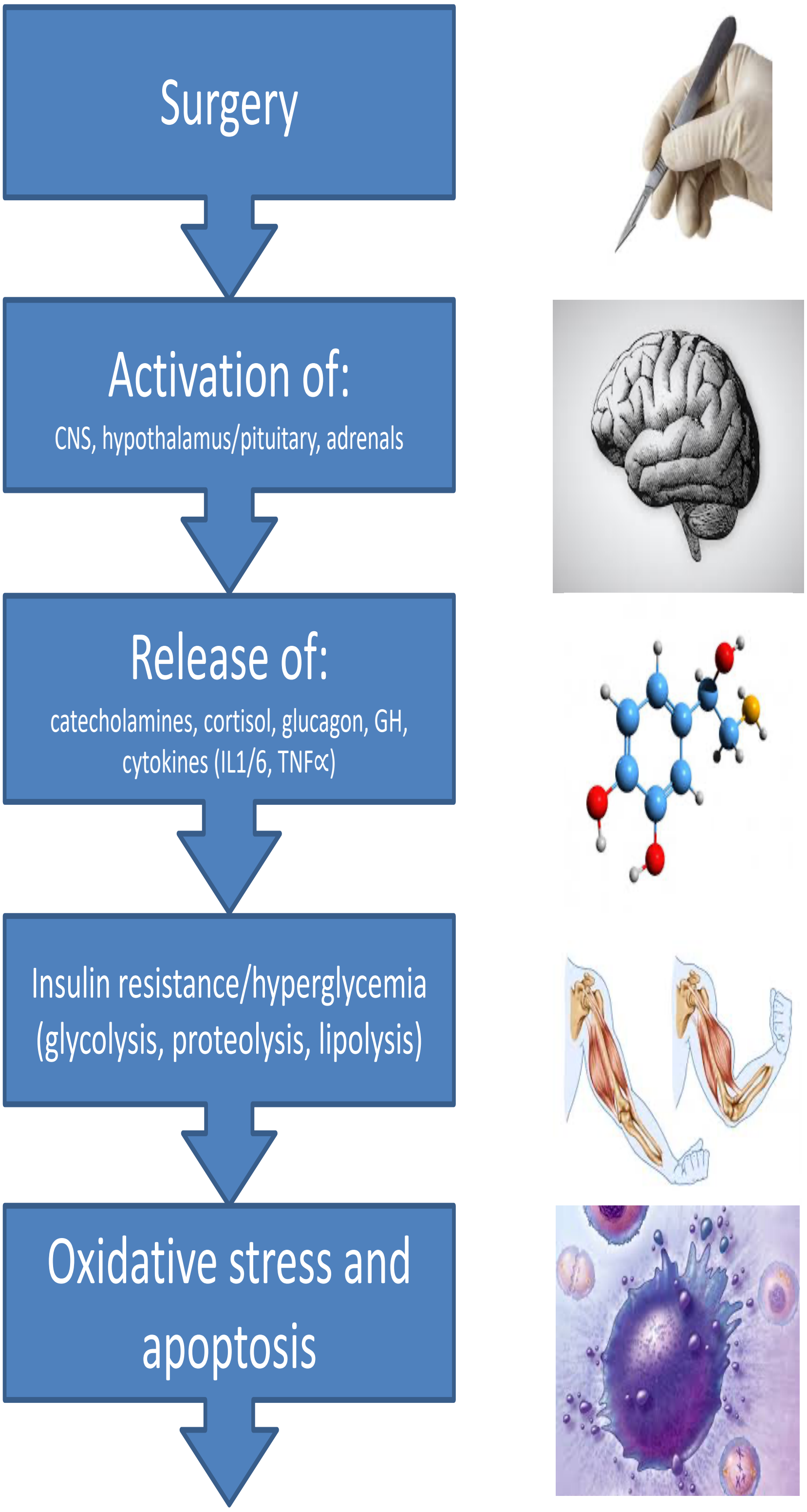



*Figure 1. Theory behind surgical stress, insulin resistance and catabolism*

## 1.3 ENHANCED RECOVERY AFTER SURGERY (ERAS)

Despite constant progress in the use of chemo- and radiotherapy, surgery is still, in most cases, the required treatment in patients with colorectal cancer[99]. Since the disease often presents at high age and patients often carry a large burden of comorbidity[14] with an increased risk of complications, improved perioperative care and postoperative recovery are important, not only for the patient, but also from a broader health economic perspective.

Historically, no general guidelines on how to treat patients undergoing colorectal surgery perioperatively have been available and perioperative care has often been dependent upon decisions from individual surgeons[100]. With the exception of nil per os and bed rest after surgery, which were considered standard of care, perioperative treatment varied widely between different centers. Furthermore, outcome recorded in databases and registers were rare entities in the past, making evaluation and interpretation of data on surgical outcomes difficult. Also, most data were retrospectively recorded by the surgeons themselves without an objective assessment of data, which resulted in reports on morbidity from colorectal surgery in varying rates ranging from 8 to 75 %[101-103].

In 1994, the concept of "Fast-track surgery" was described for the first time in the literature[104] and in the late nineties Henrik Kehlet and coworkers in Denmark presented a multimodal interventional approach in colorectal surgery aiming to reduce surgical stress and enhance postoperative recovery[105-107]. Further publications by the Danish group showed that it was possible to discharge patients from hospital as soon as 48 hours after major colorectal surgery[108] compared to LOS within traditional care up to 14 days.

These initial publications together with an increasing interest in enhanced recovery among surgeons and anesthesiologists across Europe lead to the foundation of the Enhanced Recovery After Surgery (ERAS) collaboration in 2000, which in turn led to the formation of the ERAS Society in 2010. The main goal with the ERAS society is to develop, spread and implement the ERAS protocol, improve surgical outcome and facilitate comparisons and analyzes of outcomes in colorectal surgery. In order to optimize this work, a common database was created[109, 110]. The ERAS Interactive Audit System (EIAS) today includes more than 80 000 patients with more than 300 perioperative variables recorded on each patient. The database allows single hospitals to benchmark against other centres within the audit system, both facilitating the implementation of ERAS programs and supporting ERAS centers in the follow-up of their own outcome data in order to continuously improve results from surgery[110]. In research, EIAS represents an important source for comparing surgical techniques and study outcomes from surgery.

Cornerstones of ERAS is evidence-based perioperative care, multidisciplinary and multi-professional approach, teamwork and continuous recording and audit of data. ERAS care relies on evidence in medical research and guidelines are continuously developed and updated, stating quality of evidence and recommendations using the GRADE validation system[111-113]. By using a multimodal interventional approach with the aim to reduce metabolic stress and insulin resistance, studies have shown reduced morbidity rates, improved recovery and shortened LOS after colorectal surgery[114-119], when comparing ERAS to traditional care. The protocol includes interventions covering the whole perioperative process starting with the first meeting with the patient in the outpatient clinic until 30 days follow up after the operation.

The most recent ERAS guidelines in colorectal surgery include 25 ERAS perioperative interventions[119], which are arranged in four subgroups: preadmission, preoperative, intraoperative and postoperative interventions. The quality level of evidence differs between different interventions and to what degree each intervention contributes to an improved total perioperative outcome is still largely unknown[120-122]. This explains why the use of all interventions still is recommended by the ERAS society. ERAS interventions, quality of evidence and recommendation grade are shown in Table 3.

Limitations in quality of research, in particular in early ERAS studies, are the majority of small conducted single-center based studies and a large variability in numbers of ERAS interventions used in various forms of ERAS protocols[101, 114]. Thus, by following the current protocol, with a predetermined number of interventions, research within the ERAS field will improve.

Another important factor that was only sparsely reported in early ERAS publications is compliance to interventions in the ERAS protocol. There are now convincing evidence that improved compliance to the protocol improves outcomes, measured as complications, overall recovery and hospital stay[123-125]. Measuring compliance to the ERAS protocol also provides detailed information on perioperative care, making comparison of different surgical approaches and techniques suitable. Since overall improved outcomes from surgery has been shown to reduce costs[126, 127], it is of great importance to constantly evaluate new surgical techniques.

In previous non-ERAS studies, the association between complications, reoperations and worse oncological outcome are well known[128-130]. In ERAS studies however, the research has focused mainly on short-term outcomes after surgery and very few publications are reporting on ERAS and long-term oncological outcome data. It is important to study the ERAS protocol and long-term outcome, since surgical stress in individuals undergoing major surgery can result in immunological, inflammatory, endocrine and metabolic changes involving increased levels of catecholamines, increased insulin resistance, elevated levels of proinflammatory cytokines and decreased immune response. These alterations may result in a pro-metastatic milieu causing increased proliferation, adhesion and migration by residual tumor cells, as well elevated number of complications and reoperations, leading to delay in chemotherapy and in the end worse oncological outcome, including increased risk of cancer recurrence[131, 132].

The ERAS concept and laparoscopic colorectal surgery have been shown to reduce postoperative morbidity and LOS[133, 134], although meta-analyses and randomized controlled trials (RCTs) show similar survival data comparing laparoscopic and open colorectal surgery[135-140].

In this context, within the research field of ERAS, at least two major questions need further investigation. First, single interventions in the ERAS protocol require further evaluation regarding the impact on the protocol as a whole. Also, current and new interventions need to be adapted to new surgical techniques such as robotic surgery. Second, most studies have so far been focusing on short-term outcomes after surgery. The effects of an ERAS-program on long-term outcome, most certainly needs further attention.

The thesis will investigate this research field and hopefully fill some of the knowledge gap concerning these questions.

*Table 3. ERAS interventions, quality of evidence/recommendation grade*[119]

| **Preadmission** | **Preoperative** | **Intraoperative** | **Postoperative** |
|---|---|---|---|
| Information *M/S* | PONV *H/S* | Standard anesthetic protocol *L/S* | No gastric tubes *H/S* |
| Optimization *L/S* | Nonsedative medication *M/S* | Euvolemia/electrolyte therapy *H/S* | Standardized analgesia *H/S* |
| Prehabilitation *L/W* | Antibiotics *H/S* | Prevent hypothermia *H/S* | Thromboprofylaxis *H/S* |
| Nutritional care *M/S* | No bowelprep in colonic surgery *H/S* | Minimally invasive surgery *H/S* | Euvolemia/electrolyte therapy *H/S* |
| Treatment of anemia *H/S* | Euvolemia/electrolyte therapy *M/S* | No drains *H/S* | Limited time of urinary drainage *H/S* |
| | Carbohydrate loading *L/S* | | Prevention of ileus *H/S* |
| | | | Glycemic control *L/S* |
| | | | Nutritional care *L/S* |
| | | | Early mobilization *M/S* |

Quality of evidence: high (*H*), moderate (*M*), low (*L*). Recommendation grade: strong (*S*), weak (*W*). Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. PONV = prevention of nausea and vomiting.

## 1.4 SELECTED ERAS INTERVENTIONS

### 1.4.1 Preadmission information and counseling

Preoperative optimization is an essential part of the ERAS protocol[119]. Although the evidence level regarding preoperative education and information is relatively low compared to other ERAS interventions, clinical experience indicates that this specific intervention is important in reducing LOS.

Advantages due to preadmission information demonstrated in studies include improved patient satisfaction, reduced pain and anxiety[141-143]. Improved outcomes in terms of LOS due to patient information have also been reported in studies[144, 145].

After surgery, the criteria that need to be fulfilled for a patient to be considered ready for discharge in the ERAS protocol are: no complications in need of hospital stay, return of bowel function (stool or flatus), mobilization out of bed > 6 h daily or preoperative level and postoperative pain controlled with oral analgesics[146]. Sometimes patients are fit for discharge without being able to leave the hospital and an up to 2-days difference has been described[109]. Common causes are relatives' concern, patient lacking social support and unable to handle stoma care.

Preoperative education should begin at the first outpatient meeting and continue throughout the patient's journey. Information can be given face-to-face, in writing or digital and should include information about tools aiding recovery and self-management, goal setting in the perioperative period, information about surgery, anaesthesia and discharge criteria[147].

### 1.4.2 Preoperative optimization

#### *1.4.2.1 Preoperative nutrition*

Preoperative malnutrition and weight loss are common in colorectal surgery[148]. Associations with increased morbidity, complication rates and worse survival are well described in the literature[119, 149, 150]. It is of great importance to identify, assess and correct malnutrition as early as possible. Screening tools using BMI, weight loss, food intake, disease severity, age and serum albumin have been developed. A universal consensus on how to assess preoperative nutritional status is lacking, but several validated scoring systems exist – Malnutrition Universal Screening Tool (MUST), Nutrition Risk Screening-2002 (NRS-2002) and Subjective Global Assessment (SGA).

Hypoalbuminemia is considered a predictor for increased morbidity and mortality after surgery, but should not by itself be regarded a marker for malnutrition, since low albumin is common in surgical patients due to systemic inflammation[151].

Enteral nutritional supplementation starting at least one week before surgery has been demonstrated to reduce postoperative complication rates. Parenteral nutrition should be reserved for patients with contraindications to oral feeding, or patients unable to meet requirements with enteral nutrition[149].

#### *1.4.2.2 Smoking and alcohol cessation*

Smoking is associated with increased mortality and morbidity rates after surgery. Complications include cardiovascular, respiratory, wound-healing and surgical site infections[152, 153]. Information on smoking cessation or counselling should start as early as possible before surgery to achieve best outcomes. Optimal duration to reverse the effects of smoking is unclear, but 4 weeks or longer has been shown to reduce postoperative complications[154, 155]. Counselling combined with nicotine replacement therapy are effective and increase smoking cessation rates[156].

Alcohol abuse and hazardous drinking are also known to increase postoperative morbidity and complication rates[157]. Similar to smoking cessation, 4 weeks of alcohol abstinence will reduce the risk of postoperative complications [158]. Information and counselling, sometimes combined with pharmacotherapy, should be initiated as soon as possible to achieve alcohol cessation.

Since smoking and alcohol cessation only entail positive effects for the patient, recommendations are strong in ERAS guidelines.

### 1.4.3 Treatment of anemia

The definition of anemia according to the World Health Organization (WHO) is a hemoglobin (Hb) level of < 120 g/L for women and < 130 g/L for men. In between 30 to 67 % of colorectal cancer patients will suffer from anemia during the course of disease[159].

In general, many factors can cause anemia, such as vitamin B12 or folate deficiency, chemotherapy and renal failure. In colorectal cancer patient however, the main contributors of anemia are chronic blood loss and anemia of chronic disease, i.e. colorectal cancer[160].

Anemia entails increased risk of complications and mortality in patients going through major surgery[161-163]. In addition, preoperative anemia is a major predictor for the need of blood transfusion during surgery, a factor linked to both an increased rate of complications after surgery and a negative impact on long-term survival[164, 165].

Thus, it is of great importance to optimize Hb levels preoperatively. This can be achieved by blood transfusion, erythropoiesis-stimulating agents (ESAs) or iron supplementation. However, since blood transfusions should be avoided and ESAs result in increased risk for thrombosis and mortality[166], iron supplementation, which are cost-effective and safe with a very low rate of serious adverse events, is the preferred choice of treatment. No negative effects on morbidity, mortality or cancer recurrence have been found with iron supplementation[167-169].

Many cancer patients may not respond to oral iron because of blood loss or chronic illness. It is also poorly tolerated due to gastrointestinal side effects. Besides having a low risk of adverse events, intravenous iron is more effective than oral iron in correcting Hb levels and should be the first treatment option in colorectal cancer patients suffering from anemia prior to surgery[119].

### 1.4.4 Bowel preparation

Mechanical bowel preparation (MBP) is known to cause dehydration and electrolyte imbalance, leading to potentially dangerous complications, particularly in elderly patients suffering from comorbidities[170, 171]. Fluid and electrolyte imbalance in the preoperative period is suggested to increase the fluid requirement in patients both during surgery and in the postoperative period, a factor known to have a negative effect on outcome[122]. Furthermore, MBP is not always successful in cleansing the bowel and surgery with a fluid-filled colon has been associated with increased complication rates[172].

In the literature, there is strong evidence that MBP does not reduce surgical site infection (SSI) rate or anastomotic leakage (AL) compared to surgery without bowel preparation[173-175]. There is no evidence whether or not MBP should be given prior to anterior resections with a defunctioning stoma. Most surgeons probably prefer MBP in order to avoid a colon full of faeces proximal to the anastomosis.

Data from observational studies in the U.S. have indicated that a combination of oral antibiotics together with systemic antibiotics and MBP reduce postoperative morbidity compared to systemic antibiotics and MBP or systemic antibiotics without MBP[176, 177]. The theory behind this concept is that systemic antibiotics administered prior to surgery does not affect intraluminal bacteria and the combination of MBP and oral antibiotics will reduce bacterial load and SSI. Although recent meta-analyses tend to support these findings[178-180], it is important to recognize that the data does not support the use of MBP per se. Thus, MBP alone with systemic antibiotics has no clinical advantage and should not be used routinely.

### 1.4.5 Perioperative fluid therapy

Perioperative fluid overload has been shown to yield impaired anastomotic healing, tissue edema and delayed gastrointestinal function, as well as increased overall morbidity and mortality rates[181-185]. In one study, morbidity has been shown to increase more than 30 % with every additional intravenous liter, compared to average distribution, administrated on the day of surgery[123]. On the other hand, receiving too small amount of fluids when fluid supply is required, will cause tissue hypoperfusion, generating poor outcomes due to hypoxia[182, 186]. Therefore, to keep an adequate perioperative fluid balance, is of key importance in order to improve outcome from surgery.

In the past, preoperative over-night fasting was considered standard of care aiming to minimize the risk of aspiration during and after surgery. Today, using ERAS principles, fasting periods before surgery are reduced to 6 hours for solid food and 2 hours for clear fluids and carbohydrate drinks[187, 188] without effect on aspiration rates[188]. Preoperative oral carbohydrate drinks administrated prior to surgery have been described to reduce insulin resistance, and improving preoperative well-being[189] and is therefore standard treatment in the ERAS protocol. However, evidence in terms of improved morbidity and mortality in large clinical studies is lacking.

A balanced intraoperative fluid therapy is used for maintaining cardiac output and tissue perfusion without generating salt and water overload. The treatment should be individualized and aim for near-zero-balance. Balanced crystalloids 1-4 ml/kg/hour during surgery will generally achieve this goal and weight gain more than 2.5 kg should be avoided[190].

In Goal-directed fluid therapy (GDFT), devices such as the transesophageal Doppler are used to administer fluid boluses to guide fluid therapy and to optimize stroke volume on the Frank-Starling curve. Improvement in stroke volume implies need for additional boluses and less responsiveness suggests that maintenance fluid infusion is enough[191]. Earlier studies have shown benefits from GDFT in terms of LOS and morbidity[192], but recently several publications have challenged these results, particularly when GDFT is used in an ERAS setting[193-195]. Thus, within ERAS protocols GDFT should be reserved for high-risk patients and/or high-risk procedures[190] only. In low-risk cases with hypotension, where fluid boluses fail to increase stroke volume, vasopressors are recommended[196].

The alternative to GDFT is reaching near-zero fluid balance by the use of standard anaesthesiological care, measuring variables such as blood loss, blood pressure, pulse, urine output and weight gain. This guidance has been shown to decrease the rate of postoperative complications if aiming at a restrictive intravenous fluid regimen compared to standard fluid management[185] and demonstrates equal postoperative outcomes compared to GDTF[181, 184, 197]. The results has been confirmed in ERAS research , where a perioperative restrictive intravenous fluid regimen is an important predictor for improved short-term outcome after colorectal surgery[123, 125, 198].

Patients should be motivated to eat and drink as soon as 4 hours after surgery[199], facilitating removal of intravenous fluid administration on the day of surgery for most patients. Loss of fluid due to vomiting and high stoma output may however need to be replaced by intravenous fluids.

A balanced crystalloid solution is preferable to 0.9% saline and colloids for both maintenance and fluid boluses. Saline is associated with hyperchloremic acidosis, a condition that could result in kidney failure and increased morbidity[190]. In the past colloids were used intraoperatively, but no significant advantages have been shown compared to crystalloids[190, 200]. Also, colloids are known to result in kidney failure and increased mortality[201, 202].

### 1.4.6 Prevention of postoperative ileus

Postoperative ileus (POI) is a state of transient prolonged gastrointestinal recovery after surgery, leading to abdominal distension, pain, vomiting and patient discomfort[203]. POI is associated with increased morbidity in terms of aspiration pneumonia, malnutrition, renal failure and increased LOS resulting in higher health care costs[204-206] and suffering for patients. Due to variations in definition of POI, incidence ranging from 2 to 61 % has been described[205].

Abdominal surgery entails a period of reduced gastrointestinal motility, proposed to be a part of the body’s response to surgical stress. This reaction can last up to 72 hours in colorectal surgery. Absence of gastrointestinal motility lasting longer than 3 days after laparoscopic surgery or 5 days after open surgery meets the criteria for prolonged postoperative ileus (PPOI)[207].

Intraoperative blood loss, opioid use, male gender, stoma formation, obesity, increasing age, duration of surgery, previous abdominal surgery and cardiac/respiratory co-morbidity[203, 208, 209] are all described as predictors for postoperative ileus in the literature.

A sufficient perioperative pain management is an important ERAS intervention, known to improve recovery[210]. Opioid-related side effects, such as urinary retention, nausea and respiratory depression, are common[211] and the relationship between opioid use and POI is well described in the literature[212]. Epidural analgesia reduces the need for opioids, while in addition implementing an inhibitory effect on the sympathetic nervous system. Both improving gastrointestinal motility[213].

In addition to the importance of not overloading patients with fluids in order to improve perioperative gastrointestinal function, laparoscopic surgery, known to improve recovery and reduce LOS[133, 134], has shown a positive impact on both gastrointestinal function and transit[214, 215].

Several prokinetic agents have been evaluated with conflicting results in studies, some data indicating improved outcomes[216], but other results showing no improvement in gastrointestinal motility[213]. Gastrografin® (Amidotrizoin acid), a radiological contrast agent, has not been found to significantly improve return of normal bowel function[217].

In contrary to what was previously thought, early enteral feeding has been found safe and feasible. One RCT demonstrated improved return of bowel function and decreased LOS when early enteral feeding was given[218]. There is no evidence of increased risk of anastomotic leakage[219] by early feeding. Chewing gum has been regarded as prokinetic, is safe and inexpensive, but has been withdrawn from the ERAS protocol since new data shows no evidence of improved outcomes[220].

### 1.4.7 Minimally invasive surgical techniques

#### *1.4.7.1 Laparoscopic surgery*

Laparoscopic colorectal surgery was introduced in the 1990s[221]. Today, the technique is adopted worldwide, with proportions of elective colorectal resections reaching beyond 90 % and conversion rates less than 10 % in dedicated centres. Thus, the rate of traditional open surgery procedures is decreasing.

Several reviews, meta-analyses and RCTs comparing laparoscopic versus open colorectal surgery show a decreased rate of complications, shorter recovery and LOS in laparoscopic surgery. In further detail, suggested advantages with laparoscopy are reduced ileus, earlier recovery of bowel function, reduced need for analgesics, fewer bleeding complications and fewer wound infections[136, 222-224]. However, despite the evidence in favour of laparoscopy, there are still opposing arguments, such as limited two-dimensional view within the pelvic cavity, poor ergonomic position, unstable instruments and long learning curve[225, 226].

In the ERAS protocol, laparoscopic surgery compared to open surgery is one of the strongest independent predictors for improved outcome. The technique has been investigated in prospective and retrospective cohorts[227], but also in two large RCTs, showing superior outcomes when combining laparoscopy and ERAS in terms of recovery and LOS[133, 134]. In the LAFA trial, laparoscopic surgery was the only independent factor leading to improved outcome in regression analysis[133].

In the early days of laparoscopic colorectal practice, concerns were raised about oncological safety. Although several studies have strongly rebutted this[136, 139, 140] in both colon and rectal laparoscopic surgery, two recent randomized trials failed to prove noninferiority comparing laparoscopy to open rectal surgery using a pathologic composite score including positive circumferential margin, distal margin negativity and completeness of total mesorectal excision (TME)[228, 229]. These worrying data, did however not translate into worse survival or higher local recurrence rate in the 3 year follow-up of these two trials[137, 138].

The MRC CLASICC trial initially showed non-significantly elevated rates of positive circumferential resection margin in laparoscopic anterior resections compared to open, but this did not translate into worse survival. The same study also demonstrated worse survival outcomes in patients with colonic cancer following conversion from laparoscopic to open surgery. Since advanced cancer was the most common reason for conversion, this might be the most likely reason explaining worse survival rates, rather than conversion *per se*[139].

#### *1.4.7.2 Robotic surgery*

In 2006, the first data on robotic total mesorectal excision (TME) for rectal cancer was published[230]. Robotic rectal surgery has since been widely introduced, aiming to overcome many of the shortcomings of traditional laparoscopy in the pelvic cavity using 3-dimensional vision, stable camera, endo-wristed instruments and eliminated tremor[231, 232]. In addition, shorter learning curves with the robotic platform compared to laparoscopy have been suggested[233, 234].

In 2018, Prete et al conducted a meta-analysis consisting of five RCTs confirming previously known data, i.e. robotic surgery is associated with longer operating time and lower rate of conversions[233].

Other recent meta-analyses describe similar short-term outcomes in terms of morbidity and LOS, with no difference considering lymph node harvest and CRM positivity [235, 236]. In 2017, a metaanalysis by Cui et al presented lower morbidity and shorter LOS in robotic surgery[237]. Shorter LOS are also shown in metaanalyses by Li et al and Simillis et al[238, 239].

However, although data of varying quality in favor of robotic surgery exists, larger studies and more robust meta-analyses have had difficulties to support these findings.

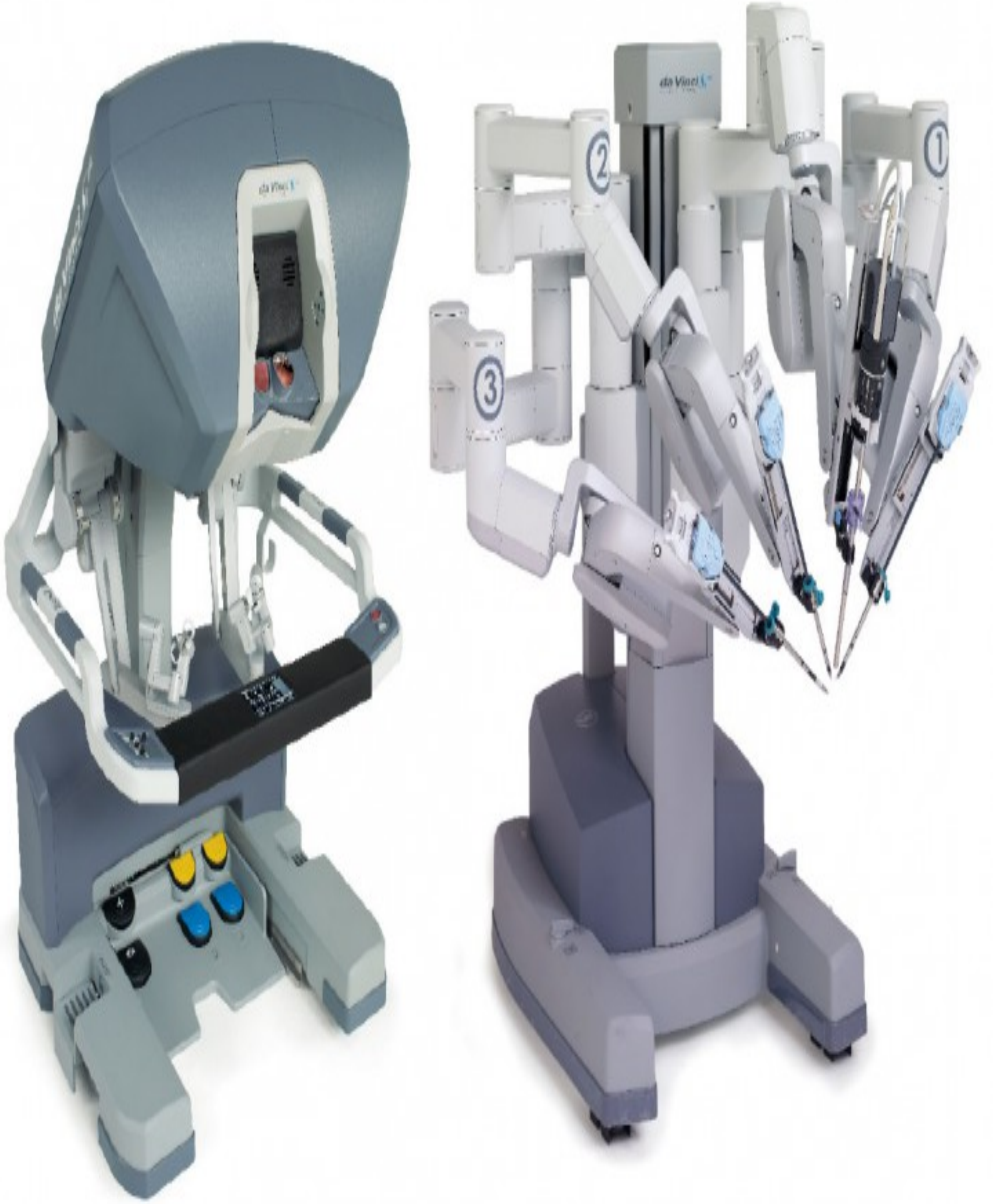
The ROLARR trial, to date the largest RCT published on this topic, revealed no differences, neither in the primary outcome conversion rate, nor in secondary outcomes comparing laparoscopic and robotic rectal surgery[240]. Corrigan et al conducted a follow-up on the ROLARR trial in 2018, adjusting for learning effects, suggesting that the equality of outcomes seen in this study might have been influenced by the surgeons' learning curve[241]. Surgeons in the laparoscopic group were more experienced compared to surgeons in the robotic group. Adjusting for the learning effect, robotic surgery seemed to have an advantage over laparoscopic surgery in terms of conversion to open surgery, when comparing equal levels of experience between robotic and laparoscopic groups.

Kim et al conducted a RCT in 2018, showing similar results as the ROLARR trial. In this study the lymph node harvest was larger, but also the estimated blood loss in robotic surgery compared to laparoscopy[242].

Studies show similar overall and disease-free survival when comparing robotic and laparoscopic rectal surgery[243, 244]. Since conversion may be a proxy for difficult surgery[245] known to result in higher complication rates and worse oncological outcome [139, 246], benefits from this aspect are yet to be proven in robotic surgery.

In the literature, there is only one retrospective cohort trial comparing short-term outcome in laparoscopic vs robotic rectal surgery within an ERAS protocol[247]. The study demonstrated significantly lower postoperative complication rates, shorter LOS, lower conversion rates favoring robotic surgery and shorter operating time favoring laparoscopic surgery.

Cost is an important issue to consider when implementing new techniques. Previous studies including the ROLARR trial demonstrated higher costs related to the robotic approach compared to the laparoscopic approach[240, 248]. The main reason for this difference is the cost of robotic instruments[249].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## 1.5 ANASTOMOTIC LEAKAGE

The rate of anastomotic leakage (AL) ranges from 0 % to 20 % in various studies conducted over the years, where highest rates are seen in colorectal/coloanal procedures[250, 251-253]. AL is one of the most feared and serious complications in colorectal surgery since it contributes not only to postoperative morbidity, mortality and reoperations, but also increases the risk of local recurrence and decreased long-term survival[254-256]. Worse outcomes in patients suffering from AL have been explained by a delay until start of adjuvant chemotherapy, metachronous and inflammation-mediated carcinogenesis or implantation of tumor cells to the anastomotic site[256].

Data from studies on AL can be difficult to interpret due to lack of a universal definition on how to describe and diagnose AL. First, there is variability in terminology. AL could be described as insufficiency, anastomotic breakdown or disruption. Terms like early or late AL also exists, depending on time to diagnosis from primary surgery. Second, diagnosis of AL could be based on clinical or radiological features, important to recognize when comparing data on AL. One of the most cited definitions, is the one proposed by Rahbari et al. Here AL is defined as a defect of the intestinal wall at the anastomotic site leading to a communication between the intra- and extraluminal compartment of the intestine. A three-grade scale was also invented. Grade A: no therapeutic interventions involved. Grade B: interventions, but no laparotomy. Grade C: interventions including laparotomy[257].

In addition to the difficulties in defining and diagnosing AL, there are data showing contradictory results for many of the proposed risk factors. Some risk factors, such as male gender, high BMI and distal anastomosis have been associated with AL repeatedly over time, whereas data concerning other proposed risk factors, such as radiotherapy and diverting stoma show diverging results. Thus, it is still of great importance to conduct studies to increase the knowledge on AL. Studies on AL within an optimized care environment such as ERAS care are lacking.

### 1.5.1 Preoperative risk factors

*Gender:*

Because of the narrow pelvis in males compared to women, there are several technical difficulties to overcome during surgery; performing total mesorectal excision (TME), transection of the bowel, and constructing the rectal anastomosis. Hence, male gender has in several studies been associated with an increased risk for AL following anterior resection (AR)[258, 259].

*BMI:*

Obesity can be measured as Body Mass Index (BMI, $kg/m^2$). A high BMI, indicating obesity, has been shown to be a significant risk factor for AL in several studies[252, 260]. Obesity contributes to an increase of the technical difficulties described above for the male gender and obese patients carry a larger burden of comorbidities proposed to increase the risk of AL, such as higher ASA score and diabetes.

*Preoperative radiotherapy:*

Preoperative radiotherapy also causes damage to healthy tissue why the risk of AL after surgery have been suggested to increase. In terms of an increased risk for AL, studies on preoperative radiotherapy have shown contradictory results. Some studies show an association between radiotherapy and AL, whereas others do not[250, 252, 253, 261, 262].

*Preoperative chemotherapy:*

Although the mechanism behind leakage in chemotherapy treatment is unknown, several studies have found a significant relationship between chemotherapy and increased AL[250, 263]. Bowel ischemia due to microembolic disease caused by chemotherapy could be one explanation. Studies on bevacizumab (Avastin) support this in theory[264, 265], although bevacizumab is given to patients in a palliative situation, not in a neoadjuvant or adjuvant setting.

*Medications:*

The use of corticosteroids has been associated with AL[266, 267] although duration and dose of corticosteroids vary considerably among studies. Reviewing the literature, it seems that high-dosage (> 20 mg/day) may increase the risk of AL, but when it comes to duration of use, there are conflicting results on the effect of AL[267].

Since the use of perioperative opioids have been shown to impair the rate of recovery, non-steroidal anti-inflammatory drugs (NSAIDs) have gained popularity. So far, there are conflicting results on a troublesome suggested association between NSAIDs and AL. Some studies state that NSAID treatment does not increase AL rate[268, 269]. However, three of the most recent meta-analyses indicate an association between NSAIDs, in particular the non-selective group, and AL[270-272].

*Malnutrition:*

Several studies report an association between malnutrition, in the literature most often estimated by preoperative weight loss, low BMI or low serum albumin concentrations, and AL[250, 273, 274]. The proposed mechanism is that malnutrition impairs collagen synthesis and fibroblast proliferation. Preoperative treatment (chemoradiotherapy) could also lead to malnutrition[274].

### 1.5.2 Intraoperative risk factors

*Anastomosis level:*

It is widely accepted that the risk of AL increases with a more distal anastomosis[253, 263], often explained by poorer blood supply, technical difficulties and increased tissue tension. Firm mechanisms behind the reason for distal anastomosis being more prone for AL are however, to a large extent, unknown.

*Number of stapler firings:*

Number of cartridges used for rectal transection is associated with increased risk of AL. The use of three or more cartridges significantly increases risk for AL after AR[275]. Multiple firings seem to cause weak spots in the stapler line making the anastomosis more fragile.

*Tumor characteristics:*

Tumor size, as well as advance stage, are associated with increased risk of AL[259, 276]. This might be due to more difficult surgery in a narrow pelvis and worse physical status in patients with a more advanced tumor stage.

*Duration of surgery:*

Intraoperative difficulties often result in prolonged duration of surgery. The reasons could be adhesions, obesity, bleeding, preoperative radiotherapy or difficulties in the stapling of an anastomosis. Thus, duration of surgery is a risk factor for AL[275].

*Intraoperative blood loss and transfusions:*

Blood loss and transfusions are identified as risk factors for AL[276]. Whether this is explained by factors related to the blood loss per se or a proxy for difficult surgery/poor operative technique remains to be confirmed.

### 1.5.3 Postoperative risk factors

*Diverting stoma:*

There is a debate on whether a diverting stoma reduces the symptoms of complications following AL (reduction of adverse effects of AL, such as peritonitis and septicemia), rather than preventing leakage per se. Some data indicates that a diverting stoma reduces the incidence of anastomotic leakage[277], while other studies fail to confirm this association[253]. The most recent meta-analysis, including only prospective RCTs, showed a significant reduction in AL and re-operation rates in patients receiving defunctioning stoma[278].

*Intestinal microbes:*

The human microbiome consists of one hundred trillion microbes. Dysbiosis among intestinal microbes might have a negative effect on diseases such as intestinal malignancies, Crohn’s disease and obesity. The intestinal flora has been proposed to influence intestinal healing and AL and although the mechanisms still are unclear an increasing amount of data in this research field is emerging. So far, Lachnospiraceae, Bacteroidaceae and Enterococcus faecalis have been associated with AL[252, 279].

# 2 AIMS

The overall aim of the thesis was to evaluate specific ERAS interventions in relation to short- and long-term outcomes after colorectal surgery.

## 2.1 PAPER I

To evaluate a possible association between restrictive perioperative fluid management and improved short-term outcome, as well as 5-year survival, in patients undergoing colorectal surgery due to cancer within an ERAS protocol.

## 2.2 PAPER II

To compare perioperative data, short-term outcome and compliance to the ERAS protocol in patients with rectal tumor operated with robotic or laparoscopic surgery within an ERAS setting.

## 2.3 PAPER III

To compare perioperative data, compliance to the ERAS protocol and short-term outcome in patients with rectal tumor from a multi-center cohort, operated with robotic, laparoscopic and open surgery within an ERAS protocol.

## 2.4 PAPER IV

To identify predictors for AL and study short-term outcomes in patients with or without AL operated with anterior resection due to rectal tumor within an ERAS protocol.

# 3 PATIENTS, MATERIAL AND METHODS

Paper I-IV were approved by the regional Ethics Committee of Stockholm and conducted in accordance with the Declaration of Helsinki of the World Medical Association.

Paper I-IV were reported according to criteria set out in the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist[280].

A $p$ value < 0.05 and/or 95 % CI not including 1 was considered statistically significant. Stata version 12.0 and 16.0 were used for statistical analysis (StataCorp, College Station, Texas, United States of America).

## 3.1 PAPER I

*Design*

Single-center retrospective cohort study with prospectively recorded data.

*Objective*

To study the impact of perioperative fluid therapy on short- and long-term outcome after colorectal surgery within an ERAS setting.

*Exposure*

The exposure variable in this study was a restrictive fluid management on the day of surgery, i.e. the first 24 hours. A restrictive fluid regimen was defined as < 3000 ml iv fluid administered. This equals the compliance threshold for colonic procedures in the ERAS database. The threshold for rectal procedures equals < 3500 ml. This difference for restrictive fluid management in colonic and rectal operations was chosen since patients operated on with rectal surgery often receive larger amounts of fluid due to longer operating times and more difficult surgery. To avoid the risk of bias in patients given excessive fluids to treat a complication, only day 0 of fluid treatment was included in the analysis of outcome. Surgical procedure was adjusted for in multivariate analysis to reduce confounding due to tumor location.

*Outcome*

The primary outcome was length of stay after surgery. Criteria for discharge were no complications requiring further hospitalization, no intravenous nutrition or fluid requirements, no need for intravenous analgesics and return of bowel function (stool or flatus). Secondary outcomes were postoperative complications, postoperative symptoms delaying discharge and

5-year overall survival. Symptoms delaying discharge included constipation, diarrhea, fever, pain, fatigue and dizziness. The follow-up time was 30 days regarding short-term outcome and five years for long-term survival.

*Study population*

Altogether 911 patients were included in the study. Data on intravenous fluid therapy on the day of surgery (day 0) were collected for 898 patients. All included patients had a colonic and/or rectal resection due to cancer and were consecutively recorded in the ERAS database between January 1, 2002 to December 31, 2007 at Ersta Hospital, Stockholm, Sweden. One hundred and fourteen perioperative variables including data on iv fluid therapy, LOS, symptoms delaying discharge, postoperative complications and 30-day mortality were prospectively recorded in the database. Date and cause of death were retrieved from the Swedish Cause of Death Registry. Data on histopathology were collected from the Swedish National Colorectal Cancer Registry and patient charts.

*Statistics and data analysis*

Unadjusted associations between categorical variables were analyzed with $\chi^2$ test or Fisher's exact test when appropriate. For continuous variables a two-tailed *t* test was conducted. Results for continuous variables were presented as mean with standard deviation (SD). Frequencies and percentage were displayed for categorical variables.

Adjustment variables in multivariate analyses were sex, age, American Society of Anaesthesiologists (ASA) physical status classification, BMI, pathology (N0/>N1) and surgical procedure (colon or rectum). Multivariate regression models were performed to test adjusted associations between exposure and short-term outcomes. Results were shown as OR and 95 % CI. Cox regression was executed to assess association between exposure and five-year survival. Results were demonstrated as HR and 95 % CI. Difference in survival with regard to exposure was tested using the Kaplan-Meier method and Log-rank test.

## 3.2 PAPER II

*Design*

Single-center retrospective cohort study with prospectively recorded data.

*Objective*

To study and compare robotic and laparoscopic rectal tumor surgery regarding perioperative data, compliance to the ERAS protocol and short-term outcome.

*Exposure*

The exposure variable in this study was surgical approach – robotic or laparoscopic rectal tumor surgery which were compared over two time periods, January 2011 to April 2014 for laparoscopic surgery and April 2014 to January 2017 for robotic surgery.

*Outcome*

The primary outcome was length of stay after surgery and secondary outcomes were postoperative complications, conversion to open surgery and compliance to the ERAS protocol.

*Study population*

The study was carried out at Danderyd Hospital, Stockholm, Sweden and included all patients who had rectal surgery between 12 January 2011 to 30 January 2017. Altogether 224 patients, 102 during the first time period and 122 during the second time period, had rectal surgery due to cancer or adenoma. One hundred and nineteen patients, 47 laparoscopic procedures during the first time period and 72 robotic procedures during the second time period were consecutively included in the study. All patients were consecutively and prospectively included in the ERAS database, recording more than 300 perioperative variables together with 21 specific ERAS interventions. A standardized ERAS protocol was used with the aim of fulfilling all 21 key ERAS variables for each patient. Data on specific clinical parameters and pathology were retrieved from patient charts. Complications were classified according to Clavien-Dindo[281].

*Statistics and data analysis*

A power analysis calculated on an estimated difference in the primary outcome (LOS) with 80 % power at a two-sided alpha of 0.05, resulted in a number needed to treat (NNT) estimate of 38 patients in each group.

Crude group comparisons between continuous variables were handled using a two-tailed *t* test or Wilcoxon's rank sum test based on variable distribution. $\chi^2$ test or Fisher's exact test were used to test associations between categorical variables when appropriate.

Adjusted associations were calculated using multiple logistic and linear regression. Adjustment variables in multivariate analyses were sex, age, ASA physical status classification, BMI, pathology (N0/>N1) and surgical procedure. Compliance data was calculated as the number of accomplished interventions divided with the total number of pre-, intra or postoperative interventions.

## 3.3 PAPER III

*Design*

Multi-center retrospective cohort study with prospectively recorded data.

*Objective*

To compare compliance to the ERAS protocol and short-term outcomes in patients operated with robotic, laparoscopic or open technique due to rectal tumor included in the Swedish part of the international ERAS database.

*Exposure*

The exposure variable was surgical approach, with robotic surgery as the reference group. All patients were analyzed according to intention-to-treat.

*Outcome*

Primary outcomes were length of stay after surgery and postoperative complications. Secondary outcomes were pre- and intraoperative compliance to the ERAS protocol, reoperations, symptoms delaying discharge (paralytic ileus, pain, diarrhea, obstipation, vomiting and urinary retention), duration of surgery and conversion to open surgery. All preparations for minimally invasive surgery were included in the operating time.

*Study population*

Validation of the Swedish part of the international ERAS database was conducted in 2019. The validation included missing values, data on accuracy and coverage. All units included in the study aimed to treat patients according to the ERAS protocol including more than 300 perioperative variables and 24 ERAS interventions. All data was prospectively and consecutively recorded. All patients operated in Sweden with anterior resection or abdominoperineal resection (APR) in centers recording data in the international database between January 1, 2010 to February 27, 2020, due to rectal tumor (benign or malignant), were included in the study (N = 3125). Eight hundred and twenty-seven patients (26.5 %) had robotic surgery, 869 patients (27.8 %) had laparoscopic surgery and 1429 patients (45.7 %) were operated on with open approach.

*Statistics and data analysis*

Power analysis was calculated on an estimated difference in length of stay between groups and 38 patients in each group was estimated to reach 80 % power with a two-sided alpha of 0.05. To compare surgical approaches regarding basic characteristics, pre- and intraoperative compliance, postoperative compliance and symptoms delaying discharge univariate regression was used. Logistic regression was used for binary variables, ordinal logistic regression for ordinal variables, linear regression for continuous variables with normal distribution and Kruskal-Wallis test for continuous variables without normal distribution.

Multivariate regression models were then used testing adjusted associations between exposure and outcome. Zero-truncated negative binomial regression for LOS, logistic regression for complications, symptoms delaying discharge, reoperations, and conversion to open surgery and linear regression for duration of surgery. Multiple imputation was used to deal with missing values[282]. Adjustment variables included in the multivariate analysis were age, gender, BMI, ASA physical status classification, alcohol abuse, previous surgery, preoperative chemoradiotherapy, severe pulmonary disease, cancer, pre- and intraoperative compliance, surgical procedure (AR or APR) and year of surgery (2010 – 2015 or 2016 – 2020).

Categorical variables were given as frequencies and percentage and continuous variables as mean with SD or median with interquartile range.

## 3.4 PAPER IV

*Design*

Multi-center retrospective cohort study with prospectively recorded data.

*Objective*

To investigate potential predictors for anastomotic leaks in patients operated with anterior resection due to rectal tumor within an ERAS protocol.

*Exposure*

The exposure variables were basic characteristics, intraoperative variables and pre- and intraoperative compliance to the ERAS protocol. All variables are listed in Table 1-3, paper IV.

*Outcome*

Anastomotic leakage (binary variable, defined and recorded as AL in the ERAS database, i.e. radiological diagnosis and/or reoperation) was primary outcome in the study. Secondary outcomes were LOS after surgery, death (30-day) and postoperative complications (30-day) regarded as potential effects of AL.

*Study population*

The study included all patients with rectal tumor (benign or malignant) operated on with AR and registered in the Swedish part of the international ERAS database between January 1, 2010 to February 27, 2020. Altogether 1900 patients operated with robotic, laparoscopic or open technique were included in the study, 155 (8.2 %) with AL and 1745 (91.8 %) without AL. Data on exposure, outcome, perioperative variables and compliance to the ERAS protocol were collected from the database.

*Statistics and data analysis*

With an estimated difference in leak rate of 5 % between two surgical approaches, at least 145 patients in each group were needed to detect an OR of 2.11 with 80 % power. Unadjusted associations between basic characteristics, intraoperative variables, pre- and intraoperative compliance and AL were tested using $\chi^2$ test or Fisher's exact test. For difference in compliance rate, Wilcoxon's rank sum test was performed. These tests were also used when analyzing univariate associations between secondary outcomes and AL. Categorical variables were presented as frequencies and percentage and continuous variables as mean and SD or median and interquartile range.

Logistic regression was used in multivariate analysis controlling for confounders. Results from multivariate analysis were presented as OR and 95 % CI. Based on prior research and univariate associations with AL in this study we included the following variables in multiple regression analysis: gender, age, BMI, ASA physical status classification, surgical approach, additional procedure, peritoneal contamination, preoperative radiotherapy, year of surgery (2010 – 2015 or 2016 – 2020), pre- and intraoperative compliance rate, duration of primary surgery and new ileostomy (yes or no).

# 4 RESULTS

## 4.1 PAPER I

Nine hundred and eleven patients were included in the study. Data on intravenous fluid therapy on the day of surgery (day 0) were collected for 898 patients. Of the patients enrolled in the study, 3.1 % had laparoscopic surgery. Basic characteristics are presented in Table 4.

*Table 4. Basic characteristics, univariate analysis*

| | **Exposed group ≤ 3000 ml (N=145)** | **Unexposed group >3000 ml (N=753)** | ***p*-value** |
|---|---|---|---|
| **Age (Years ± SD)** | 69.3±12.6 | 69.3±11.5 | 0.516[a] |
| **Gender (M/F)** | 51/94 | 393/360 | <0.005[b] |
| **BMI ± SD** | 24.8±4.3 | 25.4±4.3 | 0.957[a] |
| **ASA I (N,%)** | 26 (19.9) | 120 (17.5) | |
| **ASAII (N,%)** | 86 (65.7) | 436 (63.6) | |
| **ASAIII (N,%)** | 19 (14.5) | 122 (17.8) | |
| **ASAIV (N,%)** | 0(0) | 8 (1.2) | 0.452[c] |
| **Preoperative metastasis (N,%)** | 11 (7.6) | 86 (11.4) | 0.172[b] |
| **Surgical procedure: colonic/rectal (N,%)** | 121/24 (83.4) | 374/379 (49.7) | <0.005[b] |

Values in parenthesis are percentages if not stated otherwise. Basic characteristics: ASA (American Society of Anesthesiologists physical status), BMI (Body mass index). [a]Two-tailed t test, [b]Pearson`s $\chi^2$ test, [c]Fisher exact test.

Since male gender and rectal surgery were associated with larger volume of iv fluids day 0 in univariate analysis, these variables were adjusted for in the multivariate analysis. When comparing T- and N-stadium of tumors, no difference could be detected when comparing exposed and unexposed groups.

Patient with > 70 % compliance to pre- and intraoperative variables received less iv fluids day 0 compared to patients with < 70 % compliance (mean ± SD, 3348 ± 913 mL vs 4985 ± 1501 mL, $p < 0.05$).

Univariate comparisons of selected postoperative outcomes are shown in Table 5.

*Table 5. Selected short- and long-term outcomes. Univariate analysis*

| | **Exposed group ≤ 3000 ml (N=145)** | **Unexposed group >3000 ml (N=753)** | ***p*-value** |
|---|---|---|---|
| **LOS, days ± SD** | 5.6±3.4 | 9.0±7.9 | <0.001[a] |
| **Post-op symptoms (N,%)** | 61 (42.0) | 455 (60.4) | <0.001[b] |
| **Post-op complications (N,%)** | 29 (20.0) | 320 (42.4) | <0.001[b] |
| **Unspecified death within 5 year (N,%)** | 31 (21.4) | 247 (32.8) | 0.006[b] |
| **CRC specific death within 5 year (N,%)** | 16 (11.0) | 154 (20.5) | 0.008[b] |

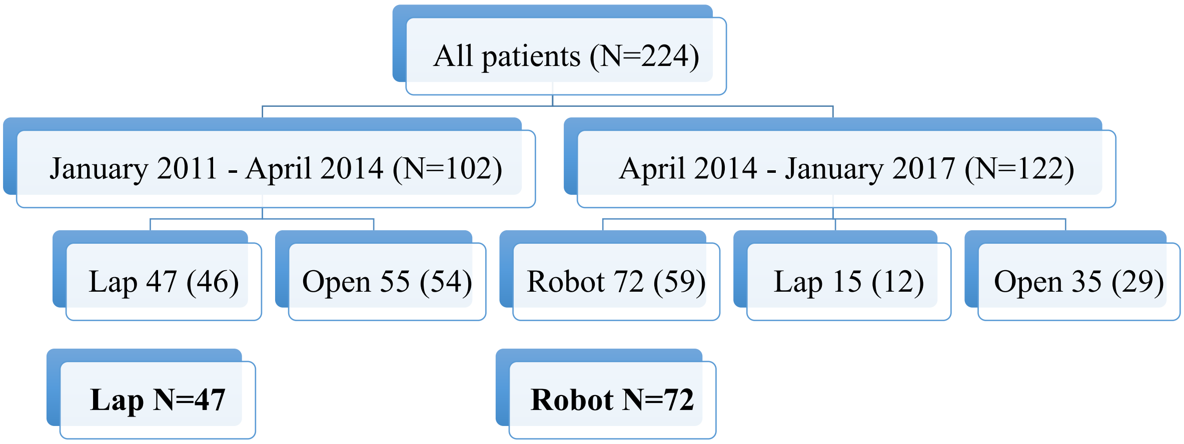
CRC = colorectal cancer. [a]Two-tailed t test, [b]Pearson`s $\chi^2$ test.

All significant differences between groups remained in multivariate analysis. The exposed group (< 3000 ml) had a lower rate of complications (OR 0.44, 95 % CI (0.28 – 0.71)), symptoms delaying discharge (OR 0.47, 95 % CI (0.32 – 0.70)) and the risk of cancer specific death was reduced with 55 % in Cox regression analysis (HR 0.45, 95 % CI (0.25 – 0.81)). Improved survival in the exposed group was demonstrated using Kaplan-Meier survival estimates, $p = 0.006$ (Log-rank test for equality of survival functions).

## 4.2 PAPER II

In all 119 patients were included in the study, 47 had laparoscopic surgery in the first time period and 72 had robotic surgery in the second time period, illustrated in Figure 2.

*Figure 2. Flow chart study cohort. N (%)*

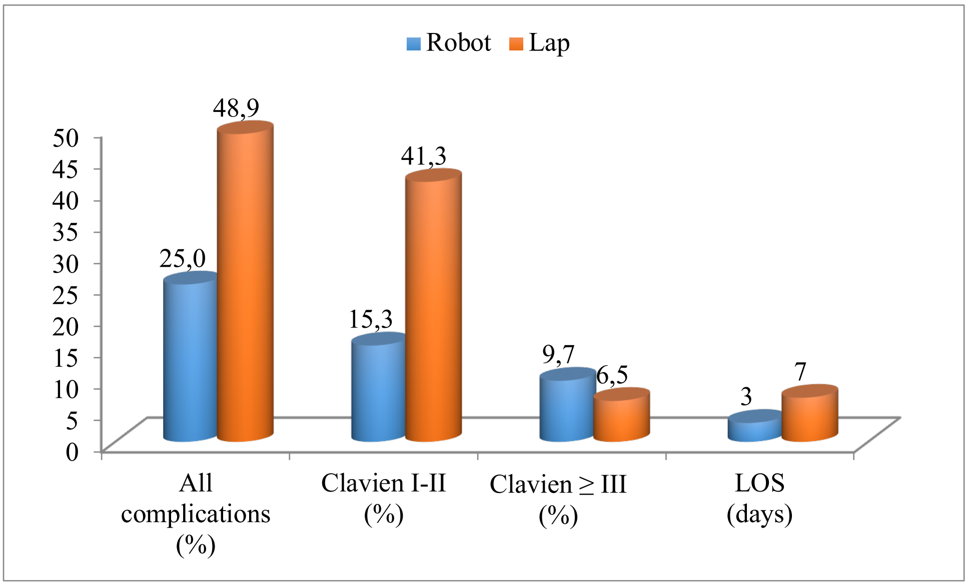



Lap = laparoscopic resection, Open = open resection, Robot = robotic resection.

There was no significant difference in compliance to pre- and intraoperative interventions of the ERAS protocol between the two groups. Patients in the robotic group were younger (65.5 (mean) ± 10.4 (SD) yrs vs 70.1 ± 12.0 yrs, $p = 0.014$), had a lower tumor height (8.5 ± 3.6 cm vs 9.8 ± 3.9 cm, $p = 0.043$) in univariate analysis, compared with patients in the laparoscopic group. Although a higher rate of patients in the robotic group compared to the laparoscopic group were treated with preoperative chemotherapy and had a higher rate of ASA class III-IV, these differences did not reach significance.

Short-term outcome demonstrated shorter length of stay in the robotic group compared to the laparoscopic group (median 3 days vs 7 days, $p < 0.001$), while length of stay for patients operated with open technique did not differ between time periods. Overall complication rate was significantly lower in the robotic group (25 % vs 49 %, $p < 0.001$), Figure 3. The differences remained significant in multivariate analysis.

*Figure 3. Complications and LOS*



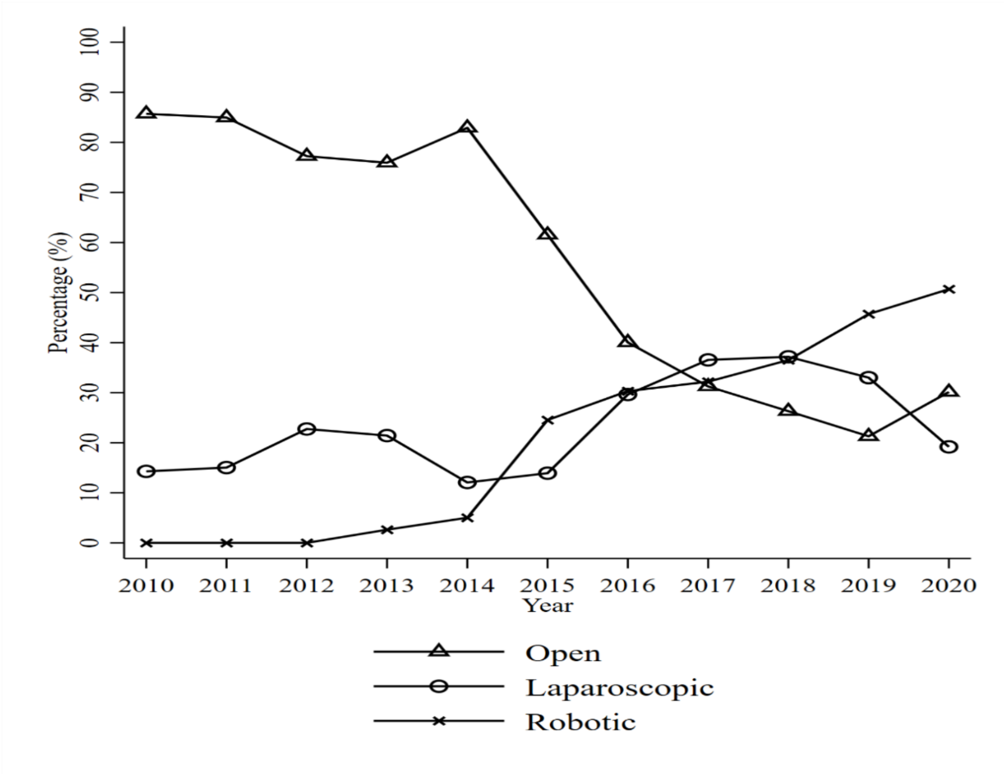

Overall complication rates were significantly lower in the robotic group (p<0.001). The difference in more serious complications Clavien ≥3, was not significant (p=0.543). LOS was significantly shorter in patients operated on with robotic technique (p<0.001).

Conversion rate to open surgery was significantly lower for the robotic technique compared to the laparoscopic technique (11.1 % vs 34.0 %, $p$ = 0.002). Overall postoperative compliance measures, regarded as outcome variables after surgery such as time to pain control, hours out of bed on the first postoperative day, time to tolerate solid food, time to withdrawal of urinary catheter and time to flatus demonstrated significantly better results in the robotic group.

## 4.3 PAPER III

Taken together 3125 patients were included in the study, 45.7 % (N = 1429) had open surgery, 27.8 % (N = 869) had laparoscopic surgery and 26.5 % (N = 827) had robotic surgery. Surgical approach stratified by time is illustrated in Figure 4.

*Figure 4. Surgical approach stratified by time*



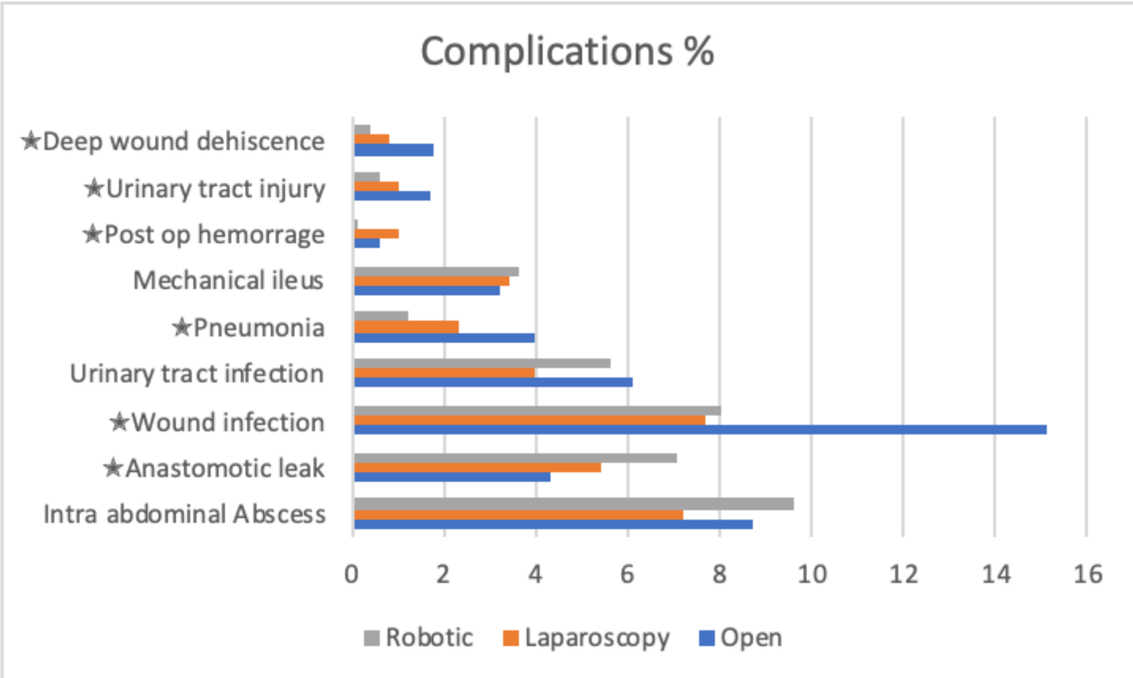

From the year 2015, the rate of open procedures decreased steadily. No robotic procedures were performed before 2013 and the proportion was increasing with time, $\chi^2(14) = 753.54$, $p < 0.001$.

Univariate analysis comparing basic characteristics showed higher rates of cancer diagnosis (97.4 % vs 95.4 %, p = 0.012), abdominoperineal resections (40.6 % vs 36.3 %, p = 0.043) and additional procedures (11.1 % vs 5.4 %, p <0.001) in the open group compared to robotic group. Previous surgery to the abdomen was more common in the open surgery compared to robotic surgery (27.0 % vs 22.7 %, p = 0.020).

Pre- and intraoperative compliance to the ERAS protocol was similar between groups, although a small, yet significant, difference was shown comparing the laparoscopic and robotic groups (93.8 % vs 92.6 %, cohen's d =0.16, p = 0.001). Analyzing postoperative compliance, regarded as outcome measures, minimally invasive surgery showed superior results in every aspect, compared to open surgery. Variables analysed were total IV volume of fluids day 0 (mL), time to passage of flatus (days), first passage of stool (days), time to tolerating solid food (days), termination of urinary drainage (days) and time to pain control with oral analgesics (days).

In multivariate analysis, adjusting for confounding, robotic surgery showed shorter length of stay compared to both laparoscopic surgery (IRR 1.14, 95 % CI (1.07, 1.21)) and open surgery (IRR 1.35, 95 % CI (1.27, 1.44)). LOS (median) was 6 days, 7 days and 9 days for robotic, laparoscopic and open surgery respectively. Conversion to open surgery was more common in the laparoscopic group (18.0 % vs 8.3 %, OR 2.58, 95 % CI (1.85, 3.60)) compared to the robotic group but the duration of surgery was longer in the robotic group, mean 5.77 hours compared to both laparoscopic surgery, mean 5.49 hours (linear coefficient -0.05, 95 % CI (-0.08, -0.01)) and open technique, mean 4.84 hours (linear coefficient -0.21, 95 % CI (-0.24, -0.17)). Univariate analysis on selected complications are illustrated in Figure 5. The overall complication rate and number of reoperations did not differ between groups in adjusted analysis. Symptoms delaying discharge were more common in open surgery compared to robotic surgery in multivariate analysis (OR 1.62, 95 % CI (1.29, 2.04)).

*Figure 5. Selected complications (%) stratified by surgical approach*




★ P value < 0.05 was considered being significant based on Bonferroni adjustment.

In univariate analysis, the rate of deep wound dehiscence (1.8 % vs 0.4 %), urinary tract injury (1.7 % vs 0.6 %), pneumonia (4,0 % vs 1.2 %) and wound infection (15.1 % vs 8.0%) was significantly higher in open compared to robotic surgery. Anastomotic leaks however, had a significantly lower rate (4.3% vs 7.1%).

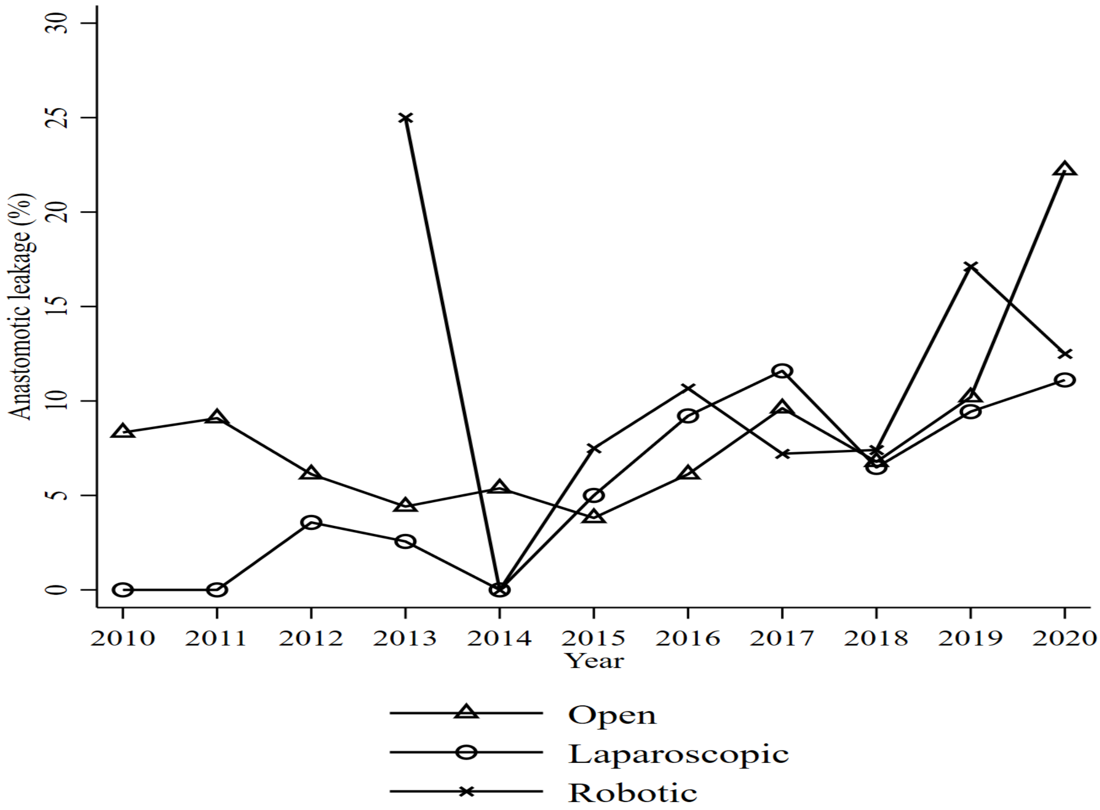
Except from a significantly higher rate of postoperative bleeding in the laparoscopic group (1% vs 0.1%) compared to the robotic group no other differences were found.

Further, 14 different types of complications were compared (not shown) without significant difference between groups with the exception of a significantly higher rate of cardiac arrythmia in the open compared with the robotic group.

## 4.4 PAPER IV

In total, 1900 patients were included in the study. The rate of anastomotic leakage was 8.2 % (N = 155). Figure 6 illustrates AL rate over time stratified on surgical technique. Surgery late in the study period (2016 – 2020) was a risk factor for AL in both uni- and multivariate analysis (9.8 % vs 5.1 %, OR 1.89, 95 % CI (1.18, 3.01)) compared to surgery early in the study period (2010 – 2015). Surgical approach was not a predictor for AL.

*Figure 6. Anastomotic leakage over time stratified by surgical approach*

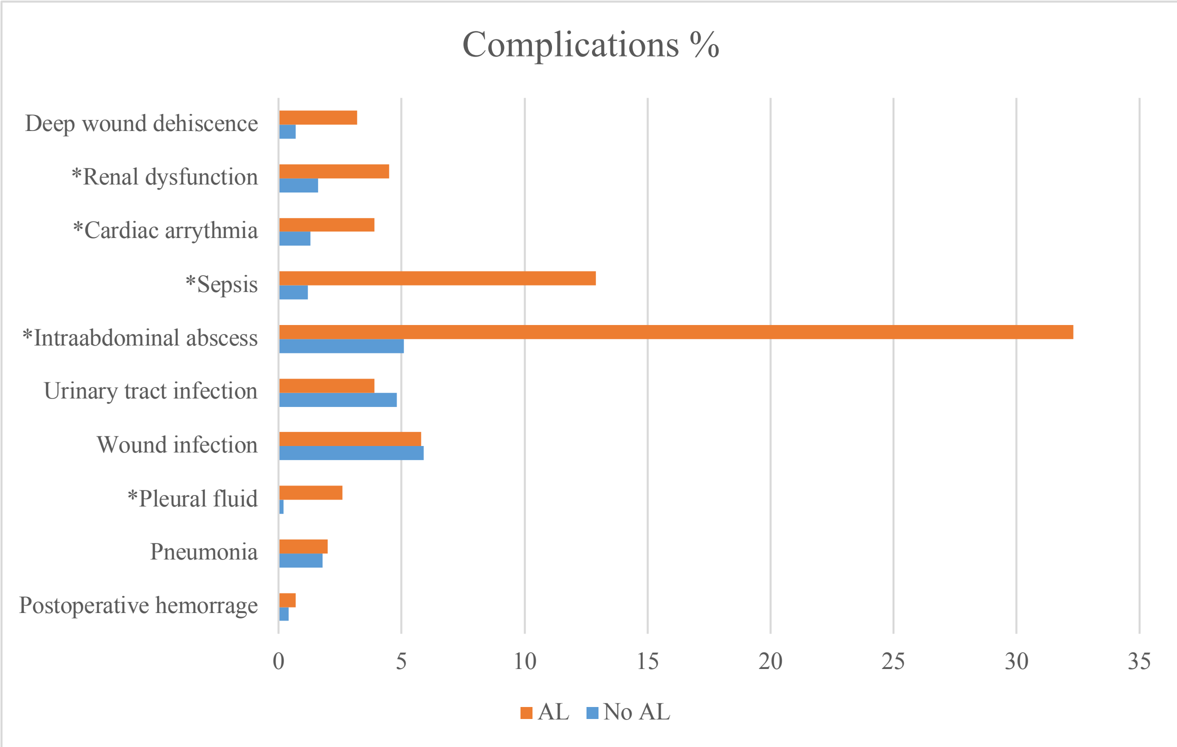



In multivariate analysis male gender (OR 1.88, 95 % CI (1.28, 2.75)), obesity (OR 1.71, 95% CI (1.04, 2.80)), peritoneal soiling (OR 1.78, 95 % CI (1.01, 3.16)) and duration of primary surgery (OR 1.13, 95 % CI (1.02, 1.24)) were all significant predictors for AL.

Overall compliance to pre- and intraoperative ERAS interventions showed no significant difference comparing AL and no AL groups (OR 0.99, 95 % CI (0.97, 1.01)). AL group demonstrated worse overall postoperative compliance (outcome) measures (data not shown).

Secondary outcomes showed worse result for patients with AL regarding major complications (63.9 % vs 5.9 %, $p$ <0.001), reoperations (69.7 % vs 6.6 %, $\chi^2$ (1) = 542.68, $p$ <0.001) and LOS (median 15 vs 7 nights, Z = -11.72, $p$ < 0.001). Selected complications are illustrated in Figure 7.

*Figure 7. Selected complications (%) stratified by presence of AL*




* P value less than 0.05 was considered significant. Further 12 complications were compared (not shown) without significant difference between groups.

# 5 DISCUSSION

## 5.1 PERIOPERATIVE FLUID THERAPY

In paper I, a single-center cohort study investigating volumes of administered perioperative fluids and outcome from surgery, the major findings were an association between a restrictive intravenous fluid regimen on the day of surgery and a decrease in length of stay after surgery, postoperative complications and symptoms delaying discharge, as well as an improved 5-year cancer specific survival.

In ERAS protocols, shown to reduce surgical stress and improving postoperative recovery[114, 118, 119], the use of a balanced or a restrictive perioperative fluid regimen have been shown to be an important independent variable for outcome[123, 125, 198].

During surgery, iv fluids can be administered either by the use of standard anaesthesiological care reaching a near-zero balance or by adopting the concept of goal directed fluid therapy (GDFT), using fluid boluses and devices such as the esophageal doppler to measure the need for fluids. The opinion on whether to use GDFT or not differs among studies[192, 194] and in the latest ERAS guidelines[119] the recommendation is that GDFT should be reserved for high-risk patients and high-risk procedures only. To reach a near-zero fluid balance using standard anaesthesiological care will thus be enough for most patients. In paper 1, GDFT was not used on any of the patients included in the study. This might, to a certain degree, contribute to the fairly large range (700 – 12900 mL) of iv fluid administered in this cohort.

In previous studies, data have shown worse short-term outcomes both when applying a liberal fluid management, as well as inducing hypovolemia[123, 181-186]. However, the definition of what is a liberal vs a restrictive or balanced fluid management varies, which makes it difficult to draw firm conclusions of an optimal perioperative fluid management. In our study, a restrictive fluid management on the day of surgery, was defined as < 3000 mL of iv fluid administered day 0 in both colonic and rectal procedures. In the ERAS database however, the definition of a restrictive, or compliant, fluid regimen differs between colonic (< 3000 mL) and rectal (< 3500 mL) procedures. All outcome data was therefore adjusted for surgical procedure in the multivariate analysis in order to avoid confounding caused by differences in iv fluid given between procedures and the fact that bowel preparation is more common in rectal surgery. Perioperative bleeding did not differ between colonic and rectal surgery in our cohort, a factor that otherwise could have had impact on the amount of fluid administered. Whether it is the threshold for fluid administration set in the ERAS protocol, or in the present study that is correct in the context of what is liberal and restrictive fluid management, can of course be questioned.

Considering the relatively long inclusion time (2002 – 2007) in this observational study, there is a possibility that a more "liberal" fluid regimen was used early in the study period compared to a more "restrictive" regimen in the late period. In 2002, standard of care was still a more "liberal" fluid regimen and to adopt ERAS principles with a more "restrictive" fluid treatment probably took several years. This time variable together with a large rate of open surgery (96.9 %), might explain the poor compliance rate (21.0 %) to the treatment of iv fluids day 0 in the present study.

In study I, all patients were treated according to a standardized ERAS protocol, including 21 perioperative interventions, at the time of inclusion. Compliance to the protocol interventions is divided into pre-, intra- and postoperative measures. Pre- and intraoperative compliance to ERAS interventions, such as preadmission counselling, use of premedication and oral intake day 0, are to a large extent independent from patient factors affecting outcome and thus included in compliance analysis. Compliance to postoperative interventions, such as time to solid food intake, time to pain control and mobilization, i.e. outcome measures from surgery, were not included in overall compliance analysis, due to possible impact from surgical outcome. In study I, patients with > 70 % compliance to pre- and intraoperative interventions received less iv fluid compared to patients with less than 70 % compliance, indicating that although the results were adjusted for confounding, a small difference in pre- and intraoperative interventions other than fluids may have had an effect on outcome.

Results presented in this study, i.e. superior short-term outcome and improved 5-year survival in patients receiving < 3000 mL iv fluid day 0 is in line with previous publications showing that increased adherence will result in improved outcomes after surgery[123, 125, 198]. The mechanisms by which ERAS protocols might have a positive effect on long-term oncological outcome are so far speculative. Theories include surgical trauma stimulating dormant remaining cancer cells or post-operative influence on the immune response[131, 132, 283-285]. Overall complications were reduced with restrictive fluid management in the present study, which is consistent with results from earlier studies on long-term follow-up that have shown postoperative complications to be associated with worse survival[286, 287].

## 5.2 MINIMALLY INVASIVE SURGERY

In paper II and III, different surgical approaches used within an ERAS setting were compared regarding compliance to the protocol and short-term outcomes. In Paper II, a single-center cohort study, comparing laparoscopic and robotic rectal tumor surgery between two time periods, the results showed a significantly shorter LOS, reduced complication rates and fewer conversions to open surgery in the robotic group. In Paper III, a multi-center retrospective cohort study of patients from all centers in Sweden recording in the International ERAS database was conducted. To our knowledge the largest observational publication comparing short-term outcome in patients undergoing robotic, laparoscopic or open rectal tumor surgery.

The results showed significantly shorter LOS in the robotic surgery group compared to laparoscopic and open surgery and lower conversion rate to open surgery in robotic vs laparoscopic surgery. Complication rates did not differ between groups in Paper III. Pre- and intraoperative compliance to the ERAS protocol was similar between groups in both studies.

Despite the fact that laparoscopic colorectal surgery was introduced 30 years ago[221] it has taken a long time to show benefits compared with traditional open surgery. Today however, summing up the level of evidence, laparoscopy show superior short-term outcomes[223, 224] and similar long-term oncological outcomes[137, 138, 222-224] compared to open surgery.

The first publication on robotic TME was published in 2006[230], since then many studies have been conducted, many of them underpowered and often of poor quality. Furthermore, no studies have investigated robotic surgery in an optimized perioperative environment, such as ERAS care.

Survival rates seem to be similar between robotic and laparoscopic rectal surgery[243, 244]. When comparing short-term outcomes, the most recent meta-analysis consisting of small RCTs, confirmed previously published results, i.e. robotic surgery is associated with longer operating time and lower rate of conversion to open surgery[233]. There are however, several meta-analyses showing improved short-term outcomes for robotic surgery[237-239], but these are often hampered by small sample sizes and low quality evidence. The ROLARR trial, to date the largest RCT published on this topic, revealed no differences in primary outcome – conversion rate, or secondary outcomes comparing laparoscopic and robotic rectal surgery[240]. However, a recent follow-up study suggested that the results shown in the ROLARR trial might have been influenced by the surgeons' learning curve, since surgeons in the laparoscopic group were more experienced than surgeons in the robotic group[241].

Similar superior short-term outcomes in favour of robotic surgery shown in paper II have been repeated in a recently published retrospective cohort trial within an ERAS setting[247]. Outcomes with such a great advantage for robotic surgery might to some extent be explained by bias and confounding due to the single center study design. The large difference in LOS between robotic and laparoscopic surgery in paper II could, to a certain extent, depend on better postoperative compliance and a lower conversion rate to open surgery but also the fact that single coworkers in the medical staff may have had an impact on the results that cannot be adjusted for. In this context, it is important to notice that median LOS in open surgery did not differ between the two time periods. The lower complication rate in robotic surgery compared to laparoscopic surgery in paper II may be biased by the same factors as in the difference in LOS, but the fact remains that robotic surgery had lower mean CRP values in the postoperative period, which indicates decreased intraoperative tissue damage. Overall, despite the risk factors for bias when analyzing results, it is of great value to know what a single-center institution can achieve, when implementing new minimally invasive techniques in an ERAS environment.

Paper III was conducted in order to investigate if the results on robotic surgery in a limited single center environment could be confirmed with a large sample size from a nationwide multicenter database. The results from paper III showed better outcomes for robotic surgery compared to laparoscopic surgery in terms of LOS and conversion rate, when these two minimalinvasive techniques were compared in relation to open surgery. When comparing robotic surgery with open surgery, all postoperative compliance measures were better in robotic surgery, explaining part of the difference in LOS in favor for the new surgical technique. However, only one postoperative compliance item, time to pain control, showed better results in robotic vs laparoscopic surgery. Since symptoms delaying discharge and complication rates were similar in both robotic and laparoscopic surgery, pain is the only factor that can explain the difference in LOS between the two groups. Superior visualization and exposure in a narrow pelvis may explain some of the difference seen in conversion rate to open surgery between robotic and laparoscopic techniques shown in papers II and III, however, potential benefits in short- and long-term due to this lower conversion rate are yet to be proven[139, 223, 246].

The longer operating time shown in robotic surgery, compared to both open and laparoscopic surgery, is not surprising, since adopting a new surgical technique takes time and includes a learning curve for all members of the team. It is important to notice that docking and set up in robotic surgery might explain some of the difference and that studies have shown a shorter learning curve in robotic surgery compared to laparoscopic surgery[234, 288]. The difference seen in operating time can be expected to decrease even further in the future.

## 5.3 ANASTOMOTIC LEAKAGE

In paper IV, a multi-center retrospective cohort study, with data from all Swedish centers recording in the international ERAS database, to our knowledge the first study investigating risk factors for anastomotic leakage in patients within an ERAS protocol, we found male gender, surgery late in the study period, obesity, peritoneal contamination and duration of surgery to be independent predictors for AL. Compared to patients with no AL patients with AL showed worse short-term outcome in length of stay, reoperations and overall complication rates. Overall pre- and intraoperative compliance to the ERAS protocol showed no difference comparing AL and non-AL patients.

It has previously been shown that short-term outcomes, including morbidity, mortality and reoperations, as well as long-term outcomes, measured as local recurrence rate and long-term survival are worse in patients suffering from AL[254, 287, 289] compared to patients without AL. However, when reviewing the literature on independent risk factors for AL, results are diverging[250, 252, 253], where the difference in study design and sample sizes between different studies might to a certain extent explain the results pointing in different directions. A factor that further complicates interpretation of data, is the lack of consensus on how to define AL since there is a vast variability in terminology, grading terms and whether an anastomotic leak should be defined as a clinical or radiological diagnosis. The EIAS database however, provides a clear definition of AL and all centers included in the current study are recording AL according to the same terms.

In accordance with the results from our study, male gender is a previously well-known risk factor for AL. Reasons for higher leak rates in males could be surgical difficulties due to a narrow pelvis or hormone-related differences impeding bowel arterial circulation[259, 290, 291]. In the same way a larger burden of comorbidities and more difficult surgery can contribute to higher AL rates in obese patients[250, 252, 253]. Intraoperative contamination has been associated with AL in previous studies[292]. Peritoneal soiling during surgery could be a sign of more difficult surgery, a factor known to result in higher AL rates. Also, the infection itself has been shown to affect the anastomosis, leading to AL[258]. Since studies show that the leak rate tend to be stable over time[251, 293], the association between AL and surgery late in our study period is difficult to explain. Registration of AL and a more accurate diagnosis, using more x-ray investigations, most certainly have improved over time and are factors that might explain part of this association. Longer duration of surgery as a risk factor for AL in the current study, is recognized in previous studies[252, 253]. Obesity, adverse events during surgery and increased bacterial exposure may contribute to this association.

Previously presented risk factors, such as smoking/alcohol, diabetes, high ASA grade and poor nutritional status, could not be identified as independent predictors in the present study[250, 274, 294, 295]. Looking into the numbers in detail, the fact that few patients in the cohort were smokers or had an alcohol abuse may only explain why this risk factor could not be identified as an independent predictor, but for the others the cause is unclear.

Age as a borderline significant protective variable against AL, shown in the current study, is somewhat surprising, since there are studies with results pointing in the opposite direction[250]. Due to the observational design of this study, we cannot exclude the possibility of selection bias, i.e. choosing healthier older patients for AR instead of permanent stoma formation. It is also possible that younger patients in this cohort might have had a more advanced stage of the disease, leading to more difficult surgery and higher AL rates, compared to the elderly.

Since increased compliance to the ERAS protocol has been shown to improve outcome from colorectal surgery, one could expect that compliance would be associated with AL as well. This association however, was not found in the current study. Only one intervention – excess of IV fluid administered intraoperatively – turned out to as a significant univariate predictor for AL, however not significant after adjustment for confounding. As expected, postoperative compliance measures, i.e. outcome variables, showed worse results in patients with AL.

## 5.4 STRENGTHS

The greatest strength in all four studies included in this thesis is that all perioperative variables that were collected for analysis had been recorded consecutively and prospectively by an independent observer into the international ERAS database, EIAS. Coverage, accuracy and rate of missing values of the data in the Swedish part of the database have recently been validated, preliminary with excellent results. Paper III and IV in this thesis are examples of multicenter studies that the ERAS society are planning for in future where large sample sizes with a high rate of coverage of a large part of a national healthcare system enables detection of data reflecting clinical reality. Although paper I and II are single center studies with smaller sample sizes, the data have been recorded and collected in two Swedish ERAS centers of excellence with well-known high rate of coverage and accuracy of data as well as excellent results after surgery.

In all four papers, overall rates of pre- and intraoperative compliance to the ERAS protocol were high and similar between the comparison groups, i.e. all patients had the same treatment before surgery. This provides equality in perioperative comparisons, reducing bias, making robust comparisons of outcomes feasible, which are considered as a major strength in all four studies. The observational design of all the studies included in this thesis facilitates the investigation of multiple covariates and outcomes. Since more than 300 perioperative variables are prospectively and consecutively recorded in the database considerably more factors can be considered compared to the gold standard study design, randomized controlled trials, that may not always reflect clinical reality.

The benefits of the access to multiple data can be exemplified by the process of analyzing associations between perioperative fluids and outcome in paper I. Since the database contains information not only on the total amount of administered fluids but also the volumes of given fluids in every step of the perioperative process, we could analyze the amount of iv fluid administered on the day of surgery separately to avoid confounding. This, since the amount of fluids administered after surgery, may be an effect of a complication during or after surgery. In multivariate analyses, we could then make stepwise adjustments for a large number of variables, including pathology and performed surgical procedure during the perioperative process. Thus, the effect of potential bias from variables such as bowel preparation, potential differences in perioperative bleeding and iv fluid administration between colonic and rectal procedures could be reduced. In paper I and II, the turnover of staff and changes in the ERAS protocol were minimal during the study period.

## 5.5 LIMITATIONS

Despite all the advantages with large retrospective cohort studies including valid data from an international database, there are many well-known pitfalls with this type of study design. In order to avoid bias, stepwise multivariate regression models were used, but should be performed carefully since this method may as well introduce bias in the results. To a certain degree, compared to randomized controlled studies, bias is always present to a larger extent in retrospective cohort studies.

Furthermore, in all papers in this thesis, there is a risk of selection bias, since there was no randomization of patients when comparing groups regarding compliance to the ERAS protocol and outcome from surgery. Although the risk of information bias might have been reduced by the fact that trained ERAS nurses performed the perioperative ERAS care and that the recording of data into the ERAS database was performed by an independent medical staff worker, one can never exclude such bias confounding the results.

Another drawback with the general use of a retrospective study design in this thesis is that it is impossible to draw firm conclusions about causal relationships. The data will provide evidence of associations, not explanatory mechanisms.

As previously discussed only pre- and intraoperative compliance were included in analysis on compliance to ERAS interventions. However, this has been a calculated strategy since the variables that sorts under postoperative compliance are affected by the outcome on the day of surgery and should be looked upon as outcome variables. This can be seen as a weakness when analyzing the ERAS protocol, but we find it the only way to interpret data correctly.

Although, we tried to minimize bias and confounding in all four studies using multivariate analysis, to the best of our knowledge and with help from statisticians, there are variables that are difficult to fully correct for. In observational studies, time is one example of such a factor. Since we reached inclusion times up to 10 years in the studies, many circumstances could have changed during the time period. The general attitudes among staff towards the ERAS protocol as a whole, but also towards different ERAS items such as iv fluid management, preop carbohydrate drink and different surgical procedures may have changed over time, thereby effecting the results in a way that is difficult to measure. The same applies to hospital staff turnover and technical progress in general. In study III and IV we included time of surgery in multivariate regression analyses aiming to exclude the impact of time as much as possible.

The single-center design used in paper I and II is in many ways troublesome, since it reduces external validity, thereby making conclusions on a broader population more difficult. There are a lot of environmental factors that are unique, and which differ between different surgical centers and since these factors are difficult to measure, the impact is unknown. In paper III and IV however, a multi-center design was used to reduce the risk of this type of bias.

Finally, cost is an important issue to consider when implementing new surgical techniques. The fact that a cost analysis was not conducted in paper III is to be considered as a major limitation of the study.

# 6 CONCLUSIONS

### Paper I

A restrictive compared to a non-restrictive intravenous fluid management (< 3000 mL vs > 3000mL) on the day of surgery was associated with improved short-term postoperative outcomes as well as improved colorectal cancer specific 5-year survival in patients with colorectal cancer operated within an ERAS protocol.

### Paper II

In a single-center setting within an ERAS protocol, robotic rectal tumor surgery is associated with shorter LOS, lower complication rates and lower conversion rate to open surgery compared to laparoscopic rectal tumor surgery.

### Paper III

In a multi-center setting within an ERAS protocol robotic rectal tumor surgery was associated with shorter LOS compared to laparoscopic and open surgery. Robotic surgery showed lower conversion rate to open surgery compared to laparoscopic surgery. Complication rates were similar between all groups. Overall, outcome measures were better in minimally invasive surgery compared to open surgery.

### Paper IV

Male gender, obesity, surgery late in the study period, peritoneal contamination and duration of surgery were found as independent predictors for anastomotic leakage in a multi-center cohort study on patients operated with a rectal resection within an ERAS program.

# 7 FUTURE PERSPECTIVES

ERAS programs are evidence-based concepts, known to reduce postoperative morbidity, enhance recovery and shorten length of stay after surgery. Today, the ERAS protocol includes 25 ERAS interventions aiming to reduce the rate of surgical stress. So far, there are however only evidence for the implementation ERAS protocol as a whole in order to improve outcome. The contribution of each individual intervention within the protocol is still largely unknown. Although increased compliance to all interventions have been shown to improve results from surgery, only a few elements - minimally invasive surgery, a balanced intravenous fluid therapy and in some studies the preoperative carbohydrate drink have been convincingly shown as independent predictors of improved outcome. Since there are strong evidence for the use of all the interventions when studied individually, outside the ERAS protocol, there is a need for further research to investigate the rate of impact of each intervention when used together in the ERAS program. There is no point in using as many interventions as possible, rather than to make the protocol user-friendly and to optimize the outcome.

Research on ERAS until today, has mainly been focused on short-term outcomes after surgery. There are very few reports on long-term oncological outcome. The theory behind the ERAS protocol in reducing surgical stress and as a possible consequence, via improved immune response, counteracting residual tumor cells and hereby reducing recurrence risk is appealing. In a few single-center studies, an association between compliance to the ERAS protocol, restrictive iv fluid management and increased colorectal cancer specific 5-year survival has been found. More studies are warranted and of special interest in this context is the role of minimally invasive surgery which in a very near future will dominate all surgery. So far, only a few studies have shown survival benefits in minimally invasive compared to open surgery, but these results have not been confirmed in meta-analyses and RCTs.

In general, long-term oncological survival is the most important outcome for patients with colorectal cancer and it is of great importance to further clarify the complex association between risk factors before surgery, choice of surgical method, and the optimization of perioperative interventions in relation to long-term oncological outcome.

One of many strengths of using the ERAS database in studies, is the prospective and consecutive recording of more than 300 perioperative variables including compliance to the protocol on each patient enrolled in the database. These parameters make research on exposures and outcomes reflecting clinical reality suitable, in a way that may not be possible in randomized controlled studies. In order to optimize the use of the database, it is important to continue the validation of EIAS in all countries included in the ERAS collaboration. After a complete validation, we can use the full potential of the international ERAS database, today including more than 80 000 patients, in designing multi-center studies with a power that by far exceeds most of the clinical studies conducted in the colorectal research history.

Globally, a major challenge for ERAS is the implementation of the protocol in developing countries around the world. ERAS has been shown to improve outcome and reduce costs in high-income countries and would be expected to do so, even in low-income countries. Since developing countries often struggle with both higher morbidity and mortality rates compared to high-income countries, the effect of implementing ERAS could have an even larger effect on outcome and costs in this part of the world. If such an implementation process will require a modification of existing protocols and guidelines or not, remains to be investigated in international pilot projects.

# 8 ACKNOWLEDGEMENTS

Att skriva en avhandling är uppenbarligen ett lagarbete. Tack till alla som har stöttat mig i detta och ett särskilt tack till:

**Ulf O Gustafsson**, huvudhandledare, vän, kollega och ett fullständigt fenomenalt bollplank i kliniken, forskningen och livet i allmänhet. Likt compliance i ett ERAS protokoll, den enskilt viktigaste faktorn till att denna bok blev skriven. Jag är Dig evigt tacksam för detta.

**Klas Pekkari**, bihandledare, vän, kollega och sektionschef. Med en otrolig bredd, visdom och yrkeskunnande har Du genom åren sporrat mig till att bli en bättre läkare och forskare. Samtalen om allt som inte har med medicin att göra är viktiga för att påminnas om vad som verkligen betyder något i livet.

**Fredrik Hjern**, bihandledare, vän och verksamhetschef. För att Du med högt ställda krav och tålamod trott på mig och tillgodosett en utveckling som jag nog själv inte ansåg möjlig när jag för dryga tio år sedan började på kliniken.

**Erik Näslund**, professor. För Din pragmatiska hållning, korta och koncisa råd och förmågan att aldrig se några problem.

**Håkan Wallén**, professor, studierektor KI DS och **Nina Ringart** handläggare KI DS. För snabba svar, hjälp med logistik och disputationsansökan.

**Greger Olsson**, min ”kirurgiske storebror”, vän, tidigare kollega och handledare under ST. Sannolikt den enskilda person som har haft störst betydelse för den kirurg och läkare jag är i dag – på gott och ont, mest gott:).

**Ulf Kressner**, vän, tidigare kollega och sektionschef. Jag är otroligt tacksam för att Du ringde upp mig den där vinterkvällen och frågade om jag ville börja jobba i Stockholm. Det har varit en ära att få jobba med Dig och att lära sig minimalinvasiv kirurgi av ”den bäste” är få förunnat – tack.

**Dan Kornfeld**, extern mentor, sektionschef på kirurgkliniken, St Görans sjukhus. Tack för att Du visade mig Kungsholmen och vidgade mina vyer, samt påpekade att min kunskaper räcker till även utanför Norrort. Sejouren blev kort på grund av olyckliga och trista omständigheter, något som gjort att jag uppskattar det jag har ännu mer än tidigare. **Johannes Croner**, vän och kollega på kirurgkliniken, St Görans sjukhus. För att Du snabbt och entusiastiskt inkluderade mig i sektionen och robotkirurgin, men tyvärr rycktes bort från jordelivet alltför tidigt.

**Josefin Segelman** och **Claes Gedda** för ovärderliga synpunkter och hjälp med första publikationen. **Olle Ljungqvist**, **Yin Xu** för Er entusiasm, kloka synpunkter, statistikhjälp och snabba återkoppling gällande studie tre och fyra.

**Mats Persborn**, **Carsten Berg**, **Karsten Offenbartl**, **Göran Simert**, **Jan-Olof Svärd** och **Anders Winbladh**. För att Ni, under mina första år som kirurg, fanns där och med stort tålamod, etisk kompass och ett enormt yrkeskunnande lärde mig hantverket från grunden.

Kollegorna på NGI-sektionen, Danderys sjukhus genom åren – **Mats Bragmark**, **Jan-Erik Åkerlund**, **Ylva Falken**, **Roger Gerjy**, **Richard Bernhoff**, **Richard Marsk**, **David Pettersson**, **Claes Anderin**, **Erik Syk**, **Mahmood Wael Mahmood**, **Karin Westberg**, **Emma Rosander**, **Ali Kiasat**, **Mikael Sundin**, **Patrik Lundström** och **Johan Styrud**. Det är en ära att få vara en del av Norra Europas bästa kolorektalsektion.

**Mamma** och **Pappa.** För att Ni alltid, med villkorslös kärlek, stöttat mig och funnits där.

**Anna**, min syster. Tack för att jag får vara en del av Ditt och Din familjs liv. Det betyder allt.

**Noah**, **Leo** och **Elise.** Ni är det bästa som har hänt mig. Älskar Er Mest.

**Helena**. Mitt livs kärlek, min klippa.

# 9 REFERENCES


1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91.

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

3. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.

4. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rodel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv22-iv40.

5. Jessup JM, McGinnis LS, Steele GD, Jr., Menck HR, Winchester DP. The National Cancer Data Base. Report on colon cancer. Cancer. 1996;78(4):918-26.

6. Thorn M, Bergstrom R, Kressner U, Sparen P, Zack M, Ekbom A. Trends in colorectal cancer incidence in Sweden 1959-93 by gender, localization, time period, and birth cohort. Cancer Causes Control. 1998;9(2):145-52.

7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.

8. Ahnen DJ, Wade SW, Jones WF, Sifri R, Mendoza Silveiras J, Greenamyer J, et al. The increasing incidence of young-onset colorectal cancer: a call to action. Mayo Clin Proc. 2014;89(2):216-24.

9. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988;319(9):525-32.

10. Strum WB. Colorectal Adenomas. N Engl J Med. 2016;374(11):1065-75.

11. Cho KR, Vogelstein B. Genetic alterations in the adenoma--carcinoma sequence. Cancer. 1992;70(6 Suppl):1727-31.

12. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759-67.

13. von Renteln D, Pohl H. Polyp Resection - Controversial Practices and Unanswered Questions. Clin Transl Gastroenterol. 2017;8(3):e76.

14. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383(9927):1490-502.

15. Parajuli R, Bjerkaas E, Tverdal A, Selmer R, Le Marchand L, Weiderpass E, et al. The increased risk of colon cancer due to cigarette smoking may be greater in women than men. Cancer Epidemiol Biomarkers Prev. 2013;22(5):862-71.

16. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. JAMA. 2008;300(23):2765-78.

17. Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. Int J Cancer. 2009;124(10):2406-15.

18. Cho E, Smith-Warner SA, Ritz J, van den Brandt PA, Colditz GA, Folsom AR, et al. Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. Ann Intern Med. 2004;140(8):603-13.

19. Fedirko V, Tramacere I, Bagnardi V, Rota M, Scotti L, Islami F, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Ann Oncol. 2011;22(9):1958-72.

20. Stone TW, McPherson M, Gail Darlington L. Obesity and Cancer: Existing and New Hypotheses for a Causal Connection. EBioMedicine. 2018;30:14-28.

21. Song M, Garrett WS, Chan AT. Nutrients, foods, and colorectal cancer prevention. Gastroenterology. 2015;148(6):1244-60 e16.

22. Robsahm TE, Aagnes B, Hjartaker A, Langseth H, Bray FI, Larsen IK. Body mass index, physical activity, and colorectal cancer by anatomical subsites: a systematic review and meta-analysis of cohort studies. Eur J Cancer Prev. 2013;22(6):492-505.

23. Koushik A, Hunter DJ, Spiegelman D, Beeson WL, van den Brandt PA, Buring JE, et al. Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. J Natl Cancer Inst. 2007;99(19):1471-83.

24. Pan P, Yu J, Wang LS. Diet and colon: what matters? Curr Opin Gastroenterol. 2019;35(2):101-6.

25. Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(20):1548-61.

26. Yuhara H, Steinmaus C, Cohen SE, Corley DA, Tei Y, Buffler PA. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? Am J Gastroenterol. 2011;106(11):1911-21; quiz 22.

27. Abdalla M, Landerholm K, Andersson P, Andersson RE, Myrelid P. Risk of Rectal Cancer After Colectomy for Patients With Ulcerative Colitis: A National Cohort Study. Clin Gastroenterol Hepatol. 2017;15(7):1055-60 e2.

28. Ekbom A, Helmick C, Zack M, Adami HO. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. Lancet. 1990;336(8711):357-9.

29. Huguet JM, Suarez P, Ferrer-Barcelo L, Ruiz L, Monzo A, Dura AB, et al. Endoscopic recommendations for colorectal cancer screening and surveillance in patients with inflammatory bowel disease: Review of general recommendations. World J Gastrointest Endosc. 2017;9(6):255-62.

30. Mehta RS, Nishihara R, Cao Y, Song M, Mima K, Qian ZR, et al. Association of Dietary Patterns With Risk of Colorectal Cancer Subtypes Classified by Fusobacterium nucleatum in Tumor Tissue. JAMA Oncol. 2017;3(7):921-7.

31. Hussan H, Clinton SK, Roberts K, Bailey MT. Fusobacterium's link to colorectal neoplasia sequenced: A systematic review and future insights. World J Gastroenterol. 2017;23(48):8626-50.

32. Bhalla A, Zulfiqar M, Bluth MH. Molecular Diagnostics in Colorectal Carcinoma: Advances and Applications for 2018. Clin Lab Med. 2018;38(2):311-42.

33. AlDubayan SH, Giannakis M, Moore ND, Han GC, Reardon B, Hamada T, et al. Inherited DNA-Repair Defects in Colorectal Cancer. Am J Hum Genet. 2018;102(3):401-14.

34. Yurgelun MB, Kulke MH, Fuchs CS, Allen BA, Uno H, Hornick JL, et al. Cancer Susceptibility Gene Mutations in Individuals With Colorectal Cancer. J Clin Oncol. 2017;35(10):1086-95.

35. Bonadona V, Bonaiti B, Olschwang S, Grandjouan S, Huiart L, Longy M, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011;305(22):2304-10.

36. ten Broeke SW, Brohet RM, Tops CM, van der Klift HM, Velthuizen ME, Bernstein I, et al. Lynch syndrome caused by germline PMS2 mutations: delineating the cancer risk. J Clin Oncol. 2015;33(4):319-25.

37. Lynch HT, Lynch PM, Lanspa SJ, Snyder CL, Lynch JF, Boland CR. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet. 2009;76(1):1-18.

38. Poulogiannis G, Frayling IM, Arends MJ. DNA mismatch repair deficiency in sporadic colorectal cancer and Lynch syndrome. Histopathology. 2010;56(2):167-79.

39. Fujiwara T, Stolker JM, Watanabe T, Rashid A, Longo P, Eshleman JR, et al. Accumulated clonal genetic alterations in familial and sporadic colorectal carcinomas with widespread instability in microsatellite sequences. Am J Pathol. 1998;153(4):1063-78.

40. Vasen HF, Blanco I, Aktan-Collan K, Gopie JP, Alonso A, Aretz S, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut. 2013;62(6):812-23.

41. Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. Am J Gastroenterol. 2014;109(8):1159-79.

42. Varesco L. Familial adenomatous polyposis: genetics and epidemiology. Tech Coloproctol. 2004;8 Suppl 2:s305-8.

43. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. Lancet. 2019;394(10207):1467-80.

44. Park SH, Lee JH, Lee SS, Kim JC, Yu CS, Kim HC, et al. CT colonography for detection and characterisation of synchronous proximal colonic lesions in patients with stenosing colorectal cancer. Gut. 2012;61(12):1716-22.

45. Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schmocker S, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol. 2012;19(7):2212-23.

46. Kaur H, Choi H, You YN, Rauch GM, Jensen CT, Hou P, et al. MR imaging for preoperative evaluation of primary rectal cancer: practical considerations. Radiographics. 2012;32(2):389-409.

47. Leufkens AM, van den Bosch MA, van Leeuwen MS, Siersema PD. Diagnostic accuracy of computed tomography for colon cancer staging: a systematic review. Scand J Gastroenterol. 2011;46(7-8):887-94.

48. Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology. 2010;257(3):674-84.

49. Mitry E, Guiu B, Cosconea S, Jooste V, Faivre J, Bouvier AM. Epidemiology, management and prognosis of colorectal cancer with lung metastases: a 30-year population-based study. Gut. 2010;59(10):1383-8.

50. Burton S, Brown G, Daniels IR, Norman AR, Mason B, Cunningham D, et al. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? Br J Cancer. 2006;94(3):351-7.

51. MacDermid E, Hooton G, MacDonald M, McKay G, Grose D, Mohammed N, et al. Improving patient survival with the colorectal cancer multi-disciplinary team. Colorectal Dis. 2009;11(3):291-5.

52. Segelman J, Singnomklao T, Hellborg H, Martling A. Differences in multidisciplinary team assessment and treatment between patients with stage IV colon and rectal cancer. Colorectal Dis. 2009;11(7):768-74.

53. Havenga K, Enker WE, Norstein J, Moriya Y, Heald RJ, van Houwelingen HC, et al. Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1411 patients. Eur J Surg Oncol. 1999;25(4):368-74.

54. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986;1(8496):1479-82.

55. Fujii S, Ishibe A, Ota M, Watanabe K, Watanabe J, Kunisaki C, et al. Randomized clinical trial of high versus low inferior mesenteric artery ligation during anterior resection for rectal cancer. BJS Open. 2018;2(4):195-202.

56. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol. 2008;26(2):303-12.

57. Caricato M, Borzomati D, Ausania F, Valeri S, Rosignoli A, Coppola R. Prognostic factors after surgery for locally recurrent rectal cancer: an overview. Eur J Surg Oncol. 2006;32(2):126-32.

58. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J Clin Oncol. 2010;28(2):272-8.

59. de Lacy FB, Chadi SA, Berho M, Heald RJ, Khan J, Moran B, et al. The Future of Rectal Cancer Surgery: A Narrative Review of an International Symposium. Surg Innov. 2018;25(5):525-35.

60. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. 2011;12(6):575-82.

61. Swedish Rectal Cancer T, Cedermark B, Dahlberg M, Glimelius B, Pahlman L, Rutqvist LE, et al. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336(14):980-7.

62. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet. 2009;373(9666):811-20.

63. Erlandsson J, Holm T, Pettersson D, Berglund A, Cedermark B, Radu C, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol. 2017;18(3):336-46.

64. Bosset JF, Calais G, Daban A, Berger C, Radosevic-Jelic L, Maingon P, et al. Preoperative chemoradiotherapy versus preoperative radiotherapy in rectal cancer patients: assessment of acute toxicity and treatment compliance. Report of the 22921 randomised trial conducted by the EORTC Radiotherapy Group. Eur J Cancer. 2004;40(2):219-24.

65. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30(16):1926-33.

66. Tamas K, Walenkamp AM, de Vries EG, van Vugt MA, Beets-Tan RG, van Etten B, et al. Rectal and colon cancer: Not just a different anatomic site. Cancer Treat Rev. 2015;41(8):671-9.

67. Blomqvist L, Glimelius B. The 'good', the 'bad', and the 'ugly' rectal cancers. Acta Oncol. 2008;47(1):5-8.

68. Sammour T, Price BA, Krause KJ, Chang GJ. Nonoperative Management or 'Watch and Wait' for Rectal Cancer with Complete Clinical Response After Neoadjuvant Chemoradiotherapy: A Critical Appraisal. Ann Surg Oncol. 2017;24(7):1904-15.

69. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandala M, Cervantes A, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi64-72.

70. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27(19):3109-16.

71. Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011;29(11):1465-71.

72. Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007;25(16):2198-204.

73. Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol. 2011;29(28):3768-74.

74. Shah MA, Renfro LA, Allegra CJ, Andre T, de Gramont A, Schmoll HJ, et al. Impact of Patient Factors on Recurrence Risk and Time Dependency of Oxaliplatin Benefit in Patients With Colon Cancer: Analysis From Modern-Era Adjuvant Studies in the Adjuvant Colon Cancer End Points (ACCENT) Database. J Clin Oncol. 2016;34(8):843-53.

75. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-9.

76. Benson AB, 3rd, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol. 2004;22(16):3408-19.

77. Quasar Collaborative G, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet. 2007;370(9604):2020-9.

78. Shinagawa T, Tanaka T, Nozawa H, Emoto S, Murono K, Kaneko M, et al. Comparison of the guidelines for colorectal cancer in Japan, the USA and Europe. Ann Gastroenterol Surg. 2018;2(1):6-12.

79. Petersen SH, Harling H, Kirkeby LT, Wille-Jorgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev. 2012(3):CD004078.

80. Breugom AJ, Swets M, Bosset JF, Collette L, Sainato A, Cionini L, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol. 2015;16(2):200-7.

81. Glynne-Jones R, Counsell N, Quirke P, Mortensen N, Maraveyas A, Meadows HM, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. Ann Oncol. 2014;25(7):1356-62.

82. Meyers BM, Cosby R, Quereshy F, Jonker D. Adjuvant Chemotherapy for Stage II and III Colon Cancer Following Complete Resection: A Cancer Care Ontario Systematic Review. Clin Oncol (R Coll Radiol). 2017;29(7):459-65.

83. Grothey A, Sobrero AF, Shields AF, Yoshino T, Paul J, Taieb J, et al. Duration of Adjuvant Chemotherapy for Stage III Colon Cancer. N Engl J Med. 2018;378(13):1177-88.

84. Cuthbertson DP, Angeles Valero Zanuy MA, Leon Sanz ML. Post-shock metabolic response. 1942. Nutr Hosp. 2001;16(5):176-82; discussion 5-6.

85. Frayn KN. Hormonal control of metabolism in trauma and sepsis. Clin Endocrinol (Oxf). 1986;24(5):577-99.

86. Deibert DC, DeFronzo RA. Epinephrine-induced insulin resistance in man. J Clin Invest. 1980;65(3):717-21.

87. Simmons PS, Miles JM, Gerich JE, Haymond MW. Increased proteolysis. An effect of increases in plasma cortisol within the physiologic range. J Clin Invest. 1984;73(2):412-20.

88. Schiekofer S, Andrassy M, Chen J, Rudofsky G, Schneider J, Wendt T, et al. Acute hyperglycemia causes intracellular formation of CML and activation of ras, p42/44 MAPK, and nuclear factor kappaB in PBMCs. Diabetes. 2003;52(3):621-33.

89. Perner A, Nielsen SE, Rask-Madsen J. High glucose impairs superoxide production from isolated blood neutrophils. Intensive Care Med. 2003;29(4):642-5.

90. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg. 1999;67(2):352-60; discussion 60-2.

91. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359-67.

92. Giannoudis PV, Dinopoulos H, Chalidis B, Hall GM. Surgical stress response. Injury. 2006;37 Suppl 5:S3-9.

93. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310(15):1591-600.

94. Biolo G, Fleming RY, Maggi SP, Nguyen TT, Herndon DN, Wolfe RR. Inverse regulation of protein turnover and amino acid transport in skeletal muscle of hypercatabolic patients. J Clin Endocrinol Metab. 2002;87(7):3378-84.

95. Schricker T, Meterissian S, Lattermann R, Adegoke OA, Marliss EB, Mazza L, et al. Anticatabolic effects of avoiding preoperative fasting by intravenous hypocaloric nutrition: a randomized clinical trial. Ann Surg. 2008;248(6):1051-9.

96. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2002;87(3):978-82.

97. Halkos ME, Puskas JD, Lattouf OM, Kilgo P, Kerendi F, Song HK, et al. Elevated preoperative hemoglobin A1c level is predictive of adverse events after coronary artery bypass surgery. J Thorac Cardiovasc Surg. 2008;136(3):631-40.

98. Gustafsson UO, Thorell A, Soop M, Ljungqvist O, Nygren J. Haemoglobin A1c as a predictor of postoperative hyperglycaemia and complications after major colorectal surgery. Br J Surg. 2009;96(11):1358-64.

99. Marijnen CA. Organ preservation in rectal cancer: have all questions been answered? Lancet Oncol. 2015;16(1):e13-22.

100. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008;248(2):189-98.

101. Wind J, Polle SW, Fung Kon Jin PH, Dejong CH, von Meyenfeldt MF, Ubbink DT, et al. Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg. 2006;93(7):800-9.

102. Serclova Z, Dytrych P, Marvan J, Nova K, Hankeova Z, Ryska O, et al. Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456). Clin Nutr. 2009;28(6):618-24.

103. Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N, Zurich Fast Track Study G. A fast-track program reduces complications and length of hospital stay after open colonic surgery. Gastroenterology. 2009;136(3):842-7.

104. Engelman RM, Rousou JA, Flack JE, 3rd, Deaton DW, Humphrey CB, Ellison LH, et al. Fast-track recovery of the coronary bypass patient. Ann Thorac Surg. 1994;58(6):1742-6.

105. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth. 1997;78(5):606-17.

106. Bardram L, Funch-Jensen P, Jensen P, Crawford ME, Kehlet H. Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. Lancet. 1995;345(8952):763-4.

107. Kehlet H, Mogensen T. Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. Br J Surg. 1999;86(2):227-30.

108. Basse L, Hjort Jakobsen D, Billesbolle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. Ann Surg. 2000;232(1):51-7.

109. Maessen J, Dejong CH, Hausel J, Nygren J, Lassen K, Andersen J, et al. A protocol is not enough to implement an enhanced recovery programme for colorectal resection. Br J Surg. 2007;94(2):224-31.

110. Currie A, Soop M, Demartines N, Fearon K, Kennedy R, Ljungqvist O. Enhanced Recovery After Surgery Interactive Audit System: 10 Years' Experience with an International Web-Based Clinical and Research Perioperative Care Database. Clin Colon Rectal Surg. 2019;32(1):75-81.

111. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490.

112. Guyatt G, Vist G, Falck-Ytter Y, Kunz R, Magrini N, Schunemann H. An emerging consensus on grading recommendations? Evid Based Med. 2006;11(1):2-4.

113. Jaeschke R, Guyatt GH, Dellinger P, Schunemann H, Levy MM, Kunz R, et al. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. BMJ. 2008;337:a744.

114. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr. 2010;29(4):434-40.

115. Lv L, Shao YF, Zhou YB. The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. Int J Colorectal Dis. 2012;27(12):1549-54.

116. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ, Delaney CP. Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. Surgery. 2011;149(6):830-40.

117. Tan SJ, Zhou F, Yui WK, Chen QY, Lin ZL, Hu RY, et al. Fast track programmes vs. traditional care in laparoscopic colorectal surgery: a meta-analysis of randomized controlled trials. Hepatogastroenterology. 2014;61(129):79-84.

118. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. JAMA Surg. 2017;152(3):292-8.

119. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS((R))) Society Recommendations: 2018. World J Surg. 2018.

120. Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr. 2005;24(3):466-77.

121. Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg. 2009;144(10):961-9.

122. Asklid D, Segelman J, Gedda C, Hjern F, Pekkari K, Gustafsson UO. The impact of perioperative fluid therapy on short-term outcomes and 5-year survival among patients undergoing colorectal cancer surgery - A prospective cohort study within an ERAS protocol. Eur J Surg Oncol. 2017;43(8):1433-9.

123. Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, Nygren J, et al. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. Arch Surg. 2011;146(5):571-7.

124. Nelson G, Kiyang LN, Crumley ET, Chuck A, Nguyen T, Faris P, et al. Implementation of Enhanced Recovery After Surgery (ERAS) Across a Provincial Healthcare System: The ERAS Alberta Colorectal Surgery Experience. World J Surg. 2016;40(5):1092-103.

125. Group EC. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. Ann Surg. 2015;261(6):1153-9.

126. Thanh NX, Chuck AW, Wasylak T, Lawrence J, Faris P, Ljungqvist O, et al. An economic evaluation of the Enhanced Recovery After Surgery (ERAS) multisite implementation program for colorectal surgery in Alberta. Can J Surg. 2016;59(6):415-21.

127. Visioni A, Shah R, Gabriel E, Attwood K, Kukar M, Nurkin S. Enhanced Recovery After Surgery for Noncolorectal Surgery?: A Systematic Review and Meta-analysis of Major Abdominal Surgery. Ann Surg. 2018;267(1):57-65.

128. Duraes LC, Stocchi L, Steele SR, Kalady MF, Church JM, Gorgun E, et al. The Relationship Between Clavien-Dindo Morbidity Classification and Oncologic Outcomes After Colorectal Cancer Resection. Ann Surg Oncol. 2018;25(1):188-96.

129. Osterman E, Glimelius B. Recurrence Risk After Up-to-Date Colon Cancer Staging, Surgery, and Pathology: Analysis of the Entire Swedish Population. Dis Colon Rectum. 2018;61(9):1016-25.

130. Aoyama T, Oba K, Honda M, Sadahiro S, Hamada C, Mayanagi S, et al. Impact of postoperative complications on the colorectal cancer survival and recurrence: analyses of pooled individual patients' data from three large phase III randomized trials. Cancer Med. 2017;6(7):1573-80.

131. Horowitz M, Neeman E, Sharon E, Ben-Eliyahu S. Exploiting the critical perioperative period to improve long-term cancer outcomes. Nat Rev Clin Oncol. 2015;12(4):213-26.

132. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative events influence cancer recurrence risk after surgery. Nat Rev Clin Oncol. 2018;15(4):205-18.

133. Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg. 2011;254(6):868-75.

134. Kennedy RH, Francis EA, Wharton R, Blazeby JM, Quirke P, West NP, et al. Multicenter randomized controlled trial of conventional versus laparoscopic surgery for

colorectal cancer within an enhanced recovery programme: EnROL. J Clin Oncol. 2014;32(17):1804-11.

135. Trastulli S, Cirocchi R, Listorti C, Cavaliere D, Avenia N, Gulla N, et al. Laparoscopic vs open resection for rectal cancer: a meta-analysis of randomized clinical trials. Colorectal Dis. 2012;14(6):e277-96.

136. Vennix S, Pelzers L, Bouvy N, Beets GL, Pierie JP, Wiggers T, et al. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev. 2014(4):CD005200.

137. Stevenson ARL, Solomon MJ, Brown CSB, Lumley JW, Hewett P, Clouston AD, et al. Disease-free Survival and Local Recurrence After Laparoscopic-assisted Resection or Open Resection for Rectal Cancer: The Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial. Ann Surg. 2018.

138. Fleshman J, Branda ME, Sargent DJ, Boller AM, George VV, Abbas MA, et al. Disease-free Survival and Local Recurrence for Laparoscopic Resection Compared With Open Resection of Stage II to III Rectal Cancer: Follow-up Results of the ACOSOG Z6051 Randomized Controlled Trial. Ann Surg. 2018.

139. Green BL, Marshall HC, Collinson F, Quirke P, Guillou P, Jayne DG, et al. Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg. 2013;100(1):75-82.

140. Jeong SY, Park JW, Nam BH, Kim S, Kang SB, Lim SB, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. Lancet Oncol. 2014;15(7):767-74.

141. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Curr Med Res Opin. 2014;30(1):149-60.

142. Hounsome J, Lee A, Greenhalgh J, Lewis SR, Schofield-Robinson OJ, Coldwell CH, et al. A systematic review of information format and timing before scheduled adult surgery for peri-operative anxiety. Anaesthesia. 2017;72(10):1265-72.

143. Ziehm S, Rosendahl J, Barth J, Strauss BM, Mehnert A, Koranyi S. Psychological interventions for acute pain after open heart surgery. Cochrane Database Syst Rev. 2017;7:CD009984.

144. Forsmo HM, Pfeffer F, Rasdal A, Ostgaard G, Mohn AC, Korner H, et al. Compliance with enhanced recovery after surgery criteria and preoperative and postoperative counselling reduces length of hospital stay in colorectal surgery: results of a randomized controlled trial. Colorectal Dis. 2016;18(6):603-11.

145. Powell R, Scott NW, Manyande A, Bruce J, Vogele C, Byrne-Davis LM, et al. Psychological preparation and postoperative outcomes for adults undergoing surgery under general anaesthesia. Cochrane Database Syst Rev. 2016(5):CD008646.

146. Asklid D, Gerjy R, Hjern F, Pekkari K, Gustafsson UO. Robotic vs laparoscopic rectal tumour surgery: a cohort study. Colorectal Dis. 2019;21(2):191-9.

147. Ardo NP, Loizzi D, Panariti S, Piccinin I, Sollitto F. Enhanced recovery pathways in thoracic surgery from Italian VATS group: nursing care program. J Thorac Dis. 2018;10(Suppl 4):S529-S34.

148. Burden ST, Hill J, Shaffer JL, Todd C. Nutritional status of preoperative colorectal cancer patients. J Hum Nutr Diet. 2010;23(4):402-7.

149. Weimann A, Braga M, Carli F, Higashiguchi T, Hubner M, Klek S, et al. ESPEN guideline: Clinical nutrition in surgery. Clin Nutr. 2017;36(3):623-50.

150. Kang CY, Halabi WJ, Chaudhry OO, Nguyen V, Pigazzi A, Carmichael JC, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA Surg. 2013;148(1):65-71.

151. Torgersen Z, Balters M. Perioperative nutrition. Surg Clin North Am. 2015;95(2):255-67.

152. Turan A, Mascha EJ, Roberman D, Turner PL, You J, Kurz A, et al. Smoking and perioperative outcomes. Anesthesiology. 2011;114(4):837-46.

153. Schmid M, Sood A, Campbell L, Kapoor V, Dalela D, Klett DE, et al. Impact of smoking on perioperative outcomes after major surgery. Am J Surg. 2015;210(2):221-9 e6.

154. Mills E, Eyawo O, Lockhart I, Kelly S, Wu P, Ebbert JO. Smoking cessation reduces postoperative complications: a systematic review and meta-analysis. Am J Med. 2011;124(2):144-54 e8.

155. Thomsen T, Villebro N, Moller AM. Interventions for preoperative smoking cessation. Cochrane Database Syst Rev. 2014(3):CD002294.

156. Hartmann-Boyce J, Stead LF, Cahill K, Lancaster T. Efficacy of interventions to combat tobacco addiction: Cochrane update of 2013 reviews. Addiction. 2014;109(9):1414-25.

157. Kork F, Neumann T, Spies C. Perioperative management of patients with alcohol, tobacco and drug dependency. Curr Opin Anaesthesiol. 2010;23(3):384-90.

158. Tonnesen H, Nielsen PR, Lauritzen JB, Moller AM. Smoking and alcohol intervention before surgery: evidence for best practice. Br J Anaesth. 2009;102(3):297-306.

159. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med. 2004;116 Suppl 7A:11S-26S.

160. Wilson MJ, van Haaren M, Harlaar JJ, Park HC, Bonjer HJ, Jeekel J, et al. Long-term prognostic value of preoperative anemia in patients with colorectal cancer: A systematic review and meta-analysis. Surg Oncol. 2017;26(1):96-104.

161. Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal A, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet. 2011;378(9800):1396-407.

162. Baron DM, Hochrieser H, Posch M, Metnitz B, Rhodes A, Moreno RP, et al. Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. Br J Anaesth. 2014;113(3):416-23.

163. Smilowitz NR, Oberweis BS, Nukala S, Rosenberg A, Zhao S, Xu J, et al. Association Between Anemia, Bleeding, and Transfusion with Long-term Mortality Following Noncardiac Surgery. Am J Med. 2016;129(3):315-23 e2.

164. Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. Ann Surg. 2012;256(2):235-44.

165. Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. Cochrane Database Syst Rev. 2006(1):CD005033.

166. Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. Lancet. 2009;373(9674):1532-42.

167. Munoz M, Gomez-Ramirez S, Martin-Montanez E, Auerbach M. Perioperative anemia management in colorectal cancer patients: a pragmatic approach. World J Gastroenterol. 2014;20(8):1972-85.

168. Evstatiev R, Marteau P, Iqbal T, Khalif IL, Stein J, Bokemeyer B, et al. FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. Gastroenterology. 2011;141(3):846-53 e1-2.

169. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant. 2006;21(2):378-82.

170. Shapira Z, Feldman L, Lavy R, Weissgarten J, Haitov Z, Halevy A. Bowel preparation: comparing metabolic and electrolyte changes when using sodium phosphate/polyethylene glycol. Int J Surg. 2010;8(5):356-8.

171. Belsey J, Epstein O, Heresbach D. Systematic review: oral bowel preparation for colonoscopy. Aliment Pharmacol Ther. 2007;25(4):373-84.

172. Mahajna A, Krausz M, Rosin D, Shabtai M, Hershko D, Ayalon A, et al. Bowel preparation is associated with spillage of bowel contents in colorectal surgery. Dis Colon Rectum. 2005;48(8):1626-31.

173. Rollins KE, Javanmard-Emamghissi H, Lobo DN. Impact of mechanical bowel preparation in elective colorectal surgery: A meta-analysis. World J Gastroenterol. 2018;24(4):519-36.

174. Guenaga KF, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. 2011(9):CD001544.

175. Toh JWT, Phan K, Ctercteko G, Pathma-Nathan N, El-Khoury T, Richardson A, et al. The role of mechanical bowel preparation and oral antibiotics for left-sided laparoscopic and open elective restorative colorectal surgery with and without faecal diversion. Int J Colorectal Dis. 2018;33(12):1781-91.

176. Morris MS, Graham LA, Chu DI, Cannon JA, Hawn MT. Oral Antibiotic Bowel Preparation Significantly Reduces Surgical Site Infection Rates and Readmission Rates in Elective Colorectal Surgery. Ann Surg. 2015;261(6):1034-40.

177. Midura EF, Jung AD, Hanseman DJ, Dhar V, Shah SA, Rafferty JF, et al. Combination oral and mechanical bowel preparations decreases complications in both right and left colectomy. Surgery. 2018;163(3):528-34.

178. Rollins KE, Javanmard-Emamghissi H, Acheson AG, Lobo DN. The Role of Oral Antibiotic Preparation in Elective Colorectal Surgery: A Meta-analysis. Ann Surg. 2019;270(1):43-58.

179. Toh JWT, Phan K, Hitos K, Pathma-Nathan N, El-Khoury T, Richardson AJ, et al. Association of Mechanical Bowel Preparation and Oral Antibiotics Before Elective Colorectal Surgery With Surgical Site Infection: A Network Meta-analysis. JAMA Netw Open. 2018;1(6):e183226.

180. McSorley ST, Steele CW, McMahon AJ. Meta-analysis of oral antibiotics, in combination with preoperative intravenous antibiotics and mechanical bowel preparation the day before surgery, compared with intravenous antibiotics and mechanical bowel preparation alone to reduce surgical-site infections in elective colorectal surgery. BJS Open. 2018;2(4):185-94.

181. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. Proc Nutr Soc. 2010;69(4):488-98.

182. Lobo DN. Fluid overload and surgical outcome: another piece in the jigsaw. Ann Surg. 2009;249(2):186-8.

183. Silva JM, Jr., de Oliveira AM, Nogueira FA, Vianna PM, Pereira Filho MC, Dias LF, et al. The effect of excess fluid balance on the mortality rate of surgical patients: a multicenter prospective study. Crit Care. 2013;17(6):R288.

184. Bundgaard-Nielsen M, Secher NH, Kehlet H. 'Liberal' vs. 'restrictive' perioperative fluid therapy--a critical assessment of the evidence. Acta Anaesthesiol Scand. 2009;53(7):843-51.

185. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg. 2003;238(5):641-8.

186. Lobo DN. Fluid, electrolytes and nutrition: physiological and clinical aspects. Proc Nutr Soc. 2004;63(3):453-66.

187. Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures: An Updated Report by the American Society of Anesthesiologists Task Force on Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration. Anesthesiology. 2017;126(3):376-93.

188. Brady M, Kinn S, Stuart P. Preoperative fasting for adults to prevent perioperative complications. Cochrane Database Syst Rev. 2003(4):CD004423.

189. Gianotti L, Biffi R, Sandini M, Marrelli D, Vignali A, Caccialanza R, et al. Preoperative Oral Carbohydrate Load Versus Placebo in Major Elective Abdominal Surgery (PROCY): A Randomized, Placebo-controlled, Multicenter, Phase III Trial. Ann Surg. 2018;267(4):623-30.

190. Thiele RH, Raghunathan K, Brudney CS, Lobo DN, Martin D, Senagore A, et al. American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) joint consensus statement on perioperative fluid management within an enhanced recovery pathway for colorectal surgery. Perioper Med (Lond). 2016;5:24.

191. Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. Br J Surg. 2006;93(9):1069-76.

192. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology. 2002;97(4):820-6.

193. Xu C, Peng J, Liu S, Huang Y, Guo X, Xiao H, et al. Goal-directed fluid therapy versus conventional fluid therapy in colorectal surgery: A meta analysis of randomized controlled trials. Int J Surg. 2018;56:264-73.

194. Rollins KE, Mathias NC, Lobo DN. Meta-analysis of goal-directed fluid therapy using transoesophageal Doppler monitoring in patients undergoing elective colorectal surgery. BJS Open. 2019;3(5):606-16.

195. Rollins KE, Lobo DN. Intraoperative Goal-directed Fluid Therapy in Elective Major Abdominal Surgery: A Meta-analysis of Randomized Controlled Trials. Ann Surg. 2016;263(3):465-76.

196. Feldheiser A, Conroy P, Bonomo T, Cox B, Garces TR, Spies C, et al. Development and feasibility study of an algorithm for intraoperative goaldirected haemodynamic management in noncardiac surgery. J Int Med Res. 2012;40(4):1227-41.

197. Srinivasa S, Taylor MH, Singh PP, Yu TC, Soop M, Hill AG. Randomized clinical trial of goal-directed fluid therapy within an enhanced recovery protocol for elective colectomy. Br J Surg. 2013;100(1):66-74.

198. Gustafsson UO, Oppelstrup H, Thorell A, Nygren J, Ljungqvist O. Adherence to the ERAS protocol is Associated with 5-Year Survival After Colorectal Cancer Surgery: A Retrospective Cohort Study. World J Surg. 2016;40(7):1741-7.

199. Lassen K, Kjaeve J, Fetveit T, Trano G, Sigurdsson HK, Horn A, et al. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. Ann Surg. 2008;247(5):721-9.

200. Yates DR, Davies SJ, Milner HE, Wilson RJ. Crystalloid or colloid for goal-directed fluid therapy in colorectal surgery. Br J Anaesth. 2014;112(2):281-9.

201. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124-34.

202. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367(20):1901-11.

203. Alhashemi M, Fiore JF, Jr., Safa N, Al Mahroos M, Mata J, Pecorelli N, et al. Incidence and predictors of prolonged postoperative ileus after colorectal surgery in the context of an enhanced recovery pathway. Surg Endosc. 2019;33(7):2313-22.

204. Cologne KG, Byers S, Rosen DR, Hwang GS, Ortega AE, Ault GT, et al. Factors Associated with a Short (<2 Days) or Long (>10 Days) Length of Stay after Colectomy: A Multivariate Analysis of over 400 Patients. Am Surg. 2016;82(10):960-3.

205. Wolthuis AM, Bislenghi G, Fieuws S, de Buck van Overstraeten A, Boeckxstaens G, D'Hoore A. Incidence of prolonged postoperative ileus after colorectal surgery: a systematic review and meta-analysis. Colorectal Dis. 2016;18(1):O1-9.

206. Iyer S, Saunders WB, Stemkowski S. Economic burden of postoperative ileus associated with colectomy in the United States. J Manag Care Pharm. 2009;15(6):485-94.

207. Bragg D, El-Sharkawy AM, Psaltis E, Maxwell-Armstrong CA, Lobo DN. Postoperative ileus: Recent developments in pathophysiology and management. Clin Nutr. 2015;34(3):367-76.

208. Ceretti AP, Maroni N, Longhi M, Giovenzana M, Santambrogio R, Barabino M, et al. Risk Factors for Prolonged Postoperative Ileus in Adult Patients Undergoing Elective Colorectal Surgery: An Observational Cohort Study. Rev Recent Clin Trials. 2018;13(4):295-304.

209. Kronberg U, Kiran RP, Soliman MS, Hammel JP, Galway U, Coffey JC, et al. A characterization of factors determining postoperative ileus after laparoscopic colectomy enables the generation of a novel predictive score. Ann Surg. 2011;253(1):78-81.

210. Scott MJ, Baldini G, Fearon KC, Feldheiser A, Feldman LS, Gan TJ, et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 1: pathophysiological considerations. Acta Anaesthesiol Scand. 2015;59(10):1212-31.

211. de Boer HD, Detriche O, Forget P. Opioid-related side effects: Postoperative ileus, urinary retention, nausea and vomiting, and shivering. A review of the literature. Best Pract Res Clin Anaesthesiol. 2017;31(4):499-504.

212. Gan TJ, Robinson SB, Oderda GM, Scranton R, Pepin J, Ramamoorthy S. Impact of postsurgical opioid use and ileus on economic outcomes in gastrointestinal surgeries. Curr Med Res Opin. 2015;31(4):677-86.

213. Chapman SJ, Pericleous A, Downey C, Jayne DG. Postoperative ileus following major colorectal surgery. Br J Surg. 2018;105(7):797-810.

214. van Bree SH, Vlug MS, Bemelman WA, Hollmann MW, Ubbink DT, Zwinderman AH, et al. Faster recovery of gastrointestinal transit after laparoscopy and fast-track care in patients undergoing colonic surgery. Gastroenterology. 2011;141(3):872-80 e1-4.

215. Schwenk W, Haase O, Neudecker J, Muller JM. Short term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev. 2005(3):CD003145.

216. Sweis I, Yegiyants SS, Cohen MN. The management of postoperative nausea and vomiting: current thoughts and protocols. Aesthetic Plast Surg. 2013;37(3):625-33.

217. Biondo S, Miquel J, Espin-Basany E, Sanchez JL, Golda T, Ferrer-Artola AM, et al. A Double-Blinded Randomized Clinical Study on the Therapeutic Effect of Gastrografin in Prolonged Postoperative Ileus After Elective Colorectal Surgery. World J Surg. 2016;40(1):206-14.

218. Boelens PG, Heesakkers FF, Luyer MD, van Barneveld KW, de Hingh IH, Nieuwenhuijzen GA, et al. Reduction of postoperative ileus by early enteral nutrition in patients undergoing major rectal surgery: prospective, randomized, controlled trial. Ann Surg. 2014;259(4):649-55.

219. de Aguilar-Nascimento JE, Goelzer J. [Early feeding after intestinal anastomoses: risks or benefits?]. Rev Assoc Med Bras (1992). 2002;48(4):348-52.

220. Atkinson C, Penfold CM, Ness AR, Longman RJ, Thomas SJ, Hollingworth W, et al. Randomized clinical trial of postoperative chewing gum versus standard care after colorectal resection. Br J Surg. 2016;103(8):962-70.

221. Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). Surg Laparosc Endosc. 1991;1(3):144-50.

222. Kang SB, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW, et al. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. Lancet Oncol. 2010;11(7):637-45.

223. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet. 2005;365(9472):1718-26.

224. van der Pas MH, Haglind E, Cuesta MA, Furst A, Lacy AM, Hop WC, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol. 2013;14(3):210-8.

225. Wexner SD, Bergamaschi R, Lacy A, Udo J, Brolmann H, Kennedy RH, et al. The current status of robotic pelvic surgery: results of a multinational interdisciplinary consensus conference. Surg Endosc. 2009;23(2):438-43.

226. Cadiere GB, Himpens J, Germay O, Izizaw R, Degueldre M, Vandromme J, et al. Feasibility of robotic laparoscopic surgery: 146 cases. World J Surg. 2001;25(11):1467-77.

227. Spanjersberg WR, van Sambeeck JD, Bremers A, Rosman C, van Laarhoven CJ. Systematic review and meta-analysis for laparoscopic versus open colon surgery with or without an ERAS programme. Surg Endosc. 2015;29(12):3443-53.

228. Fleshman J, Branda M, Sargent DJ, Boller AM, George V, Abbas M, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes: The ACOSOG Z6051 Randomized Clinical Trial. JAMA. 2015;314(13):1346-55.

229. Stevenson AR, Solomon MJ, Lumley JW, Hewett P, Clouston AD, Gebski VJ, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: The ALaCaRT Randomized Clinical Trial. JAMA. 2015;314(13):1356-63.

230. Pigazzi A, Ellenhorn JD, Ballantyne GH, Paz IB. Robotic-assisted laparoscopic low anterior resection with total mesorectal excision for rectal cancer. Surg Endosc. 2006;20(10):1521-5.

231. Katsuno H, Hanai T, Masumori K, Koide Y, Ashida K, Matsuoka H, et al. Robotic Surgery for Rectal Cancer: Operative Technique and Review of the Literature. J Anus Rectum Colon. 2020;4(1):14-24.

232. Hoshino N, Sakamoto T, Hida K, Sakai Y. Robotic versus laparoscopic surgery for rectal cancer: an overview of systematic reviews with quality assessment of current evidence. Surg Today. 2019;49(7):556-70.

233. Prete FP, Pezzolla A, Prete F, Testini M, Marzaioli R, Patriti A, et al. Robotic Versus Laparoscopic Minimally Invasive Surgery for Rectal Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Ann Surg. 2018;267(6):1034-46.

234. D'Annibale A, Pernazza G, Monsellato I, Pende V, Lucandri G, Mazzocchi P, et al. Total mesorectal excision: a comparison of oncological and functional outcomes between robotic and laparoscopic surgery for rectal cancer. Surg Endosc. 2013;27(6):1887-95.

235. Lee SH, Kim DH, Lim SW. Robotic versus laparoscopic intersphincteric resection for low rectal cancer: a systematic review and meta-analysis. Int J Colorectal Dis. 2018;33(12):1741-53.

236. Ohtani H, Maeda K, Nomura S, Shinto O, Mizuyama Y, Nakagawa H, et al. Meta-analysis of Robot-assisted Versus Laparoscopic Surgery for Rectal Cancer. In Vivo. 2018;32(3):611-23.

237. Cui Y, Li C, Xu Z, Wang Y, Sun Y, Xu H, et al. Robot-assisted versus conventional laparoscopic operation in anus-preserving rectal cancer: a meta-analysis. Ther Clin Risk Manag. 2017;13:1247-57.

238. Li L, Zhang W, Guo Y, Wang X, Yu H, Du B, et al. Robotic Versus Laparoscopic Rectal Surgery for Rectal Cancer: A Meta-Analysis of 7 Randomized Controlled Trials. Surg Innov. 2019;26(4):497-504.

239. Simillis C, Lal N, Thoukididou SN, Kontovounisios C, Smith JJ, Hompes R, et al. Open Versus Laparoscopic Versus Robotic Versus Transanal Mesorectal Excision for Rectal Cancer: A Systematic Review and Network Meta-analysis. Ann Surg. 2019;270(1):59-68.

240. Jayne D, Pigazzi A, Marshall H, Croft J, Corrigan N, Copeland J, et al. Effect of Robotic-Assisted vs Conventional Laparoscopic Surgery on Risk of Conversion to Open Laparotomy Among Patients Undergoing Resection for Rectal Cancer: The ROLARR Randomized Clinical Trial. JAMA. 2017;318(16):1569-80.

241. Corrigan N, Marshall H, Croft J, Copeland J, Jayne D, Brown J. Exploring and adjusting for potential learning effects in ROLARR: a randomised controlled trial comparing robotic-assisted vs. standard laparoscopic surgery for rectal cancer resection. Trials. 2018;19(1):339.

242. Kim MJ, Park SC, Park JW, Chang HJ, Kim DY, Nam BH, et al. Robot-assisted Versus Laparoscopic Surgery for Rectal Cancer: A Phase II Open Label Prospective Randomized Controlled Trial. Ann Surg. 2018;267(2):243-51.

243. Li X, Wang T, Yao L, Hu L, Jin P, Guo T, et al. The safety and effectiveness of robot-assisted versus laparoscopic TME in patients with rectal cancer: A meta-analysis and systematic review. Medicine (Baltimore). 2017;96(29):e7585.

244. Park EJ, Cho MS, Baek SJ, Hur H, Min BS, Baik SH, et al. Long-term oncologic outcomes of robotic low anterior resection for rectal cancer: a comparative study with laparoscopic surgery. Ann Surg. 2015;261(1):129-37.

245. Baek JH, McKenzie S, Garcia-Aguilar J, Pigazzi A. Oncologic outcomes of robotic-assisted total mesorectal excision for the treatment of rectal cancer. Ann Surg. 2010;251(5):882-6.

246. Rottoli M, Bona S, Rosati R, Elmore U, Bianchi PP, Spinelli A, et al. Laparoscopic rectal resection for cancer: effects of conversion on short-term outcome and survival. Ann Surg Oncol. 2009;16(5):1279-86.

247. Crippa J, Grass F, Dozois EJ, Mathis KL, Merchea A, Colibaseanu DT, et al. Robotic Surgery for Rectal Cancer Provides Advantageous Outcomes Over Laparoscopic Approach: Results From a Large Retrospective Cohort. Ann Surg. 2020.

248. Baek SJ, Kim SH, Cho JS, Shin JW, Kim J. Robotic versus conventional laparoscopic surgery for rectal cancer: a cost analysis from a single institute in Korea. World J Surg. 2012;36(11):2722-9.

249. Quijano Y, Nunez-Alfonsel J, Ielpo B, Ferri V, Caruso R, Duran H, et al. Robotic versus laparoscopic surgery for rectal cancer: a comparative cost-effectiveness study. Tech Coloproctol. 2020;24(3):247-54.

250. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg. 2015;102(5):462-79.

251. van Rooijen SJ, Huisman D, Stuijvenberg M, Stens J, Roumen RMH, Daams F, et al. Intraoperative modifiable risk factors of colorectal anastomotic leakage: Why surgeons and anesthesiologists should act together. Int J Surg. 2016;36(Pt A):183-200.

252. Sciuto A, Merola G, De Palma GD, Sodo M, Pirozzi F, Bracale UM, et al. Predictive factors for anastomotic leakage after laparoscopic colorectal surgery. World J Gastroenterol. 2018;24(21):2247-60.

253. Kawada K, Sakai Y. Preoperative, intraoperative and postoperative risk factors for anastomotic leakage after laparoscopic low anterior resection with double stapling technique anastomosis. World J Gastroenterol. 2016;22(25):5718-27.

254. Gessler B, Eriksson O, Angenete E. Diagnosis, treatment, and consequences of anastomotic leakage in colorectal surgery. Int J Colorectal Dis. 2017;32(4):549-56.

255. Bashir Mohamed K, Hansen CH, Krarup PM, Fransgard T, Madsen MT, Gogenur I. The impact of anastomotic leakage on recurrence and long-term survival in patients with colonic cancer: A systematic review and meta-analysis. Eur J Surg Oncol. 2020;46(3):439-47.

256. Foppa C, Ng SC, Montorsi M, Spinelli A. Anastomotic leak in colorectal cancer patients: New insights and perspectives. Eur J Surg Oncol. 2020;46(6):943-54.

257. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery. 2010;147(3):339-51.

258. Peeters KC, Tollenaar RA, Marijnen CA, Klein Kranenbarg E, Steup WH, Wiggers T, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg. 2005;92(2):211-6.

259. Park JS, Choi GS, Kim SH, Kim HR, Kim NK, Lee KY, et al. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision: the Korean laparoscopic colorectal surgery study group. Ann Surg. 2013;257(4):665-71.

260. Yamamoto S, Fujita S, Akasu T, Inada R, Moriya Y, Yamamoto S. Risk factors for anastomotic leakage after laparoscopic surgery for rectal cancer using a stapling technique. Surg Laparosc Endosc Percutan Tech. 2012;22(3):239-43.

261. Kobayashi M, Mohri Y, Ohi M, Inoue Y, Araki T, Okita Y, et al. Risk factors for anastomotic leakage and favorable antimicrobial treatment as empirical therapy for intra-abdominal infection in patients undergoing colorectal surgery. Surg Today. 2014;44(3):487-93.

262. Chang JS, Keum KC, Kim NK, Baik SH, Min BS, Huh H, et al. Preoperative chemoradiotherapy effects on anastomotic leakage after rectal cancer resection: a propensity score matching analysis. Ann Surg. 2014;259(3):516-21.

263. Qu H, Liu Y, Bi DS. Clinical risk factors for anastomotic leakage after laparoscopic anterior resection for rectal cancer: a systematic review and meta-analysis. Surg Endosc. 2015;29(12):3608-17.

264. Saif MW, Elfiky A, Salem RR. Gastrointestinal perforation due to bevacizumab in colorectal cancer. Ann Surg Oncol. 2007;14(6):1860-9.

265. Heinzerling JH, Huerta S. Bowel perforation from bevacizumab for the treatment of metastatic colon cancer: incidence, etiology, and management. Curr Surg. 2006;63(5):334-7.

266. Suding P, Jensen E, Abramson MA, Itani K, Wilson SE. Definitive risk factors for anastomotic leaks in elective open colorectal resection. Arch Surg. 2008;143(9):907-11; discussion 11-2.

267. Eriksen TF, Lassen CB, Gogenur I. Treatment with corticosteroids and the risk of anastomotic leakage following lower gastrointestinal surgery: a literature survey. Colorectal Dis. 2014;16(5):O154-60.

268. Rutegard M, Westermark S, Kverneng Hultberg D, Haapamaki M, Matthiessen P, Rutegard J. Non-Steroidal Anti-Inflammatory Drug Use and Risk of Anastomotic Leakage after Anterior Resection: A Protocol-Based Study. Dig Surg. 2016;33(2):129-35.

269. Kverneng Hultberg D, Angenete E, Lydrup ML, Rutegard J, Matthiessen P, Rutegard M. Nonsteroidal anti-inflammatory drugs and the risk of anastomotic leakage after anterior resection for rectal cancer. Eur J Surg Oncol. 2017;43(10):1908-14.

270. Jamjittrong S, Matsuda A, Matsumoto S, Kamonvarapitak T, Sakurazawa N, Kawano Y, et al. Postoperative non-steroidal anti-inflammatory drugs and anastomotic leakage after gastrointestinal anastomoses: Systematic review and meta-analysis. Ann Gastroenterol Surg. 2020;4(1):64-75.

271. Modasi A, Pace D, Godwin M, Smith C, Curtis B. NSAID administration post colorectal surgery increases anastomotic leak rate: systematic review/meta-analysis. Surg Endosc. 2019;33(3):879-85.

272. Smith SA, Roberts DJ, Lipson ME, Buie WD, MacLean AR. Postoperative Nonsteroidal Anti-inflammatory Drug Use and Intestinal Anastomotic Dehiscence: A Systematic Review and Meta-Analysis. Dis Colon Rectum. 2016;59(11):1087-97.

273. Kumar A, Daga R, Vijayaragavan P, Prakash A, Singh RK, Behari A, et al. Anterior resection for rectal carcinoma - risk factors for anastomotic leaks and strictures. World J Gastroenterol. 2011;17(11):1475-9.

274. Yamano T, Yoshimura M, Kobayashi M, Beppu N, Hamanaka M, Babaya A, et al. Malnutrition in rectal cancer patients receiving preoperative chemoradiotherapy is common and associated with treatment tolerability and anastomotic leakage. Int J Colorectal Dis. 2016;31(4):877-84.

275. Kim CW, Baek SJ, Hur H, Min BS, Baik SH, Kim NK. Anastomotic Leakage After Low Anterior Resection for Rectal Cancer Is Different Between Minimally Invasive Surgery and Open Surgery. Ann Surg. 2016;263(1):130-7.

276. Katsuno H, Shiomi A, Ito M, Koide Y, Maeda K, Yatsuoka T, et al. Comparison of symptomatic anastomotic leakage following laparoscopic and open low anterior resection for rectal cancer: a propensity score matching analysis of 1014 consecutive patients. Surg Endosc. 2016;30(7):2848-56.

277. Matthiessen P, Hallbook O, Rutegard J, Simert G, Sjodahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg. 2007;246(2):207-14.

278. Phan K, Oh L, Ctercteko G, Pathma-Nathan N, El Khoury T, Azam H, et al. Does a stoma reduce the risk of anastomotic leak and need for re-operation following low anterior resection for rectal cancer: systematic review and meta-analysis of randomized controlled trials. J Gastrointest Oncol. 2019;10(2):179-87.

279. Gaines S, Shao C, Hyman N, Alverdy JC. Gut microbiome influences on anastomotic leak and recurrence rates following colorectal cancer surgery. Br J Surg. 2018;105(2):e131-e41.

280. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495-9.

281. Dindo D, Hahnloser D, Clavien PA. Quality assessment in surgery: riding a lame horse. Ann Surg. 2010;251(4):766-71.

282. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-99.

283. Belizon A, Balik E, Feingold DL, Bessler M, Arnell TD, Forde KA, et al. Major abdominal surgery increases plasma levels of vascular endothelial growth factor: open more so than minimally invasive methods. Ann Surg. 2006;244(5):792-8.

284. Bird NC, Mangnall D, Majeed AW. Biology of colorectal liver metastases: A review. J Surg Oncol. 2006;94(1):68-80.

285. Faist E, Schinkel C, Zimmer S. Update on the mechanisms of immune suppression of injury and immune modulation. World J Surg. 1996;20(4):454-9.

286. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg. 2005;242(3):326-41; discussion 41-3.

287. Hain E, Maggiori L, Manceau G, Mongin C, Prost AlDJ, Panis Y. Oncological impact of anastomotic leakage after laparoscopic mesorectal excision. Br J Surg. 2017;104(3):288-95.

288. Huang YM, Huang YJ, Wei PL. Outcomes of robotic versus laparoscopic surgery for mid and low rectal cancer after neoadjuvant chemoradiation therapy and the effect of learning curve. Medicine (Baltimore). 2017;96(40):e8171.

289. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg. 2011;253(5):890-9.

290. Sparreboom CL, van Groningen JT, Lingsma HF, Wouters M, Menon AG, Kleinrensink GJ, et al. Different Risk Factors for Early and Late Colorectal Anastomotic Leakage in a Nationwide Audit. Dis Colon Rectum. 2018;61(11):1258-66.

291. Ba ZF, Yokoyama Y, Toth B, Rue LW, 3rd, Bland KI, Chaudry IH. Gender differences in small intestinal endothelial function: inhibitory role of androgens. Am J Physiol Gastrointest Liver Physiol. 2004;286(3):G452-7.

292. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg. 2006;202(3):439-44.

293. Meyer J, Naiken S, Christou N, Liot E, Toso C, Buchs NC, et al. Reducing anastomotic leak in colorectal surgery: The old dogmas and the new challenges. World J Gastroenterol. 2019;25(34):5017-25.

294. Sorensen LT, Jorgensen T, Kirkeby LT, Skovdal J, Vennits B, Wille-Jorgensen P. Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. Br J Surg. 1999;86(7):927-31.

295. Richards CH, Campbell V, Ho C, Hayes J, Elliott T, Thompson-Fawcett M. Smoking is a major risk factor for anastomotic leak in patients undergoing low anterior resection. Colorectal Dis. 2012;14(5):628-33.